

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
3 July 2003 (03.07.2003)

PCT

(10) International Publication Number  
**WO 03/053946 A1**

(51) International Patent Classification<sup>7</sup>: C07D 277/82,  
491/08, 417/14, 417/12, A61K 31/428, 31/425

(21) International Application Number: PCT/EP02/13770

(22) International Filing Date: 5 December 2002 (05.12.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
01129272.9 12 December 2001 (12.12.2001) EP

(71) Applicant: F. HOFFMANN-LA ROCHE AG [CH/CH];  
124 Grenzacherstrasse, CH-4070 Basel (CH).

(72) Inventors: FLOHR, Alexander; St. Galler-Ring 142,  
CH-4054 Basel (CH). JAKOB-ROETNE, Roland;  
Oberer Baselblick 37, 79595 Inzlingen (DE). NOR-  
CROSS, Roger, David; Alte Saline 20, CH-4310  
Rheinfelden (CH). RIEMER, Claus; Optizstrasse 5,  
79110 Freiburg (DE).

(74) Agent: POPPE, Regina; 124 Grenzacherstrasse,  
CH-4070 Basle (CH).

(81) Designated States (national): AE, AG, AL, AM, AT, AU,  
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,  
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,  
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,  
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,  
MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG,  
SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU,  
ZA, ZM, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM,  
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),  
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),  
European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,  
ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK,  
TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ,  
GW, ML, MR, NE, SN, TD, TG).

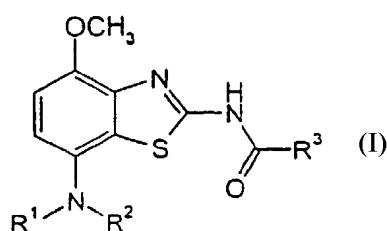
Published:

— with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 03/053946 A1

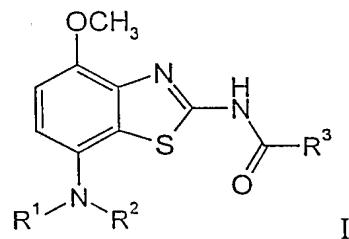
(54) Title: 7-AMINO-BENZOTHIAZOLE DERIVATIVES AS ADENOSINE RECEPTOR LIGANDS



(57) Abstract: The present invention relates to the compounds of the general formula (I). It has been found that the compounds of general formula (I) are adenosine receptor ligands. Specifically, the compounds of the present invention have a good affinity to the A<sub>2A</sub>-receptor and they are therefore useful in the treatment of diseases, related to this receptor.

## 7-AMINO-BENZOTHIAZOLE DERIVATIVES AS ADENOSINE RECEPTOR LIGANDS

The present invention relates to compounds of the general formula



wherein

- 5    R<sup>1</sup>, R<sup>2</sup> are independently from each other hydrogen, lower alkyl, C<sub>3-6</sub>-cycloalkyl, tetrahydropyran-2,3 or 4-yl, piperidin-4-yl, optionally substituted by lower alkyl, -(CH<sub>2</sub>)<sub>n</sub>-O-lower alkyl, -(CH<sub>2</sub>)<sub>n</sub>-NR'R'', -C(O)-lower alkyl, -(CH<sub>2</sub>)<sub>n</sub>-C(O)-lower alkyl, -(CH<sub>2</sub>)<sub>n</sub>-C(O)-C<sub>3-6</sub>-cycloalkyl, -(CH<sub>2</sub>)<sub>n</sub>-C(O)-NR'R'', -(CH<sub>2</sub>)<sub>n</sub>-phenyl, optionally substituted by lower alkyl, lower alkoxy or NR'R'' or is
  - 10    -(CH<sub>2</sub>)<sub>n</sub>-pyridinyl, optionally substituted by lower alkyl, lower alkoxy or NR'R'', or is -(CH<sub>2</sub>)<sub>n</sub>-morpholinyl, -(CH<sub>2</sub>)<sub>n</sub>-tetrahydropyran-2,3 or 4-yl, -(CH<sub>2</sub>)<sub>n</sub>-piperidin-1 or 4-yl, optionally substituted by lower alkyl, or is
  - 15    -C(O)-C<sub>5,6</sub>-cycloalkyl, -C(O)-tetrahydropyran-2,3 or 4-yl, -C(O)-morpholinyl, -C(O)-piperidin-1-yl or -C(O)-pyrrolidin-1-yl, or R<sup>1</sup> and R<sup>2</sup> form together with the N atom to which they are attached the ring 2-oxa-5-aza-bicyclo[2.2.1]hept-5-yl or an azetidinyl ring, optionally substituted by lower alkyl or lower alkoxy;
  - 20    R<sup>3</sup> is lower alkoxy, phenyl, optionally substituted by halogen, -(CH<sub>2</sub>)<sub>n</sub>-halogen, or by -(CH<sub>2</sub>)<sub>n</sub>-N(R')-(CH<sub>2</sub>)<sub>n+1</sub>-O-lower alkyl, or is pyridinyl, optionally substituted by lower alkyl, halogen or by morpholinyl or is morpholinyl, piperidin-1-yl, disubstituted in the 4 position by lower alkyl and -(CH<sub>2</sub>)<sub>n</sub>-OH, or is 2-aza-bicyclo[2.2.2]octane;
- n is 1 or 2;

- 2 -

R'/R" are independently from each other hydrogen or lower alkyl or together may form with the N atom an azetidinyl-, pyrrolidinyl- or piperidinyl group;

and to pharmaceutically acceptable acid addition salts thereof.

It has surprisingly been found that the compounds of general formula I are  
5 adenosine receptor ligands. Specifically, the compounds of the present invention have a good affinity to the A<sub>2A</sub>-receptor and a high selectivity to the A<sub>1</sub>- and A<sub>3</sub> receptors.

Adenosine modulates a wide range of physiological functions by interacting with specific cell surface receptors. The potential of adenosine receptors as drug targets was first reviewed in 1982. Adenosine is related both structurally and metabolically to the bioactive  
10 nucleotides adenosine triphosphate (ATP), adenosine diphosphate (ADP), adenosine monophosphate (AMP) and cyclic adenosine monophosphate (cAMP); to the biochemical methylating agent S-adenosyl-L-methionine (SAM); and structurally to the coenzymes NAD, FAD and coenzym A; and to RNA. Together adenosine and these related compounds are important in the regulation of many aspects of cellular metabolism and in the modulation  
15 of different central nervous system activities.

The receptores for adenosine have been classified as A<sub>1</sub>, A<sub>2A</sub>, A<sub>2B</sub> and A<sub>3</sub> receptors, belonging to the family of G protein-coupled receptors. Activation of adenosine receptors by adenosine initiates signal transduction mechanism. These mechanisms are dependent on the receptor associated G protein. Each of the adenosine receptor subtyps has been  
20 classically characterised by the adenylate cyclase effector system, which utilises cAMP as a second messenger. The A<sub>1</sub> and A<sub>3</sub> receptors, coupled with G<sub>i</sub> proteins inhibit adenylate cyclase, leading to a decrease in cellular cAMP levels, while A<sub>2A</sub> and A<sub>2B</sub> receptors couple to G<sub>s</sub> proteins and activate adenylate cyclase, leading to an increase in cellular cAMP levels. It is known that the A<sub>1</sub> receptor system include the activation of phospholipase C and  
25 modulation of both potassium and calcium ion channels. The A<sub>3</sub> subtype, in addition to its association with adenylate cyclase, also stimulates phospholipase C and so activates calcium ion channels.

The A<sub>1</sub> receptor (326-328 amino acids) was cloned from various species (canine, human, rat, dog, chick, bovine, guinea-pig) with 90-95 % sequence identify among the  
30 mammalian species. The A<sub>2A</sub> receptor (409-412 amino acids) was cloned from canine, rat, human, guinea pig and mouse. The A<sub>2B</sub> receptor (332 amino acids) was cloned from human and mouse with 45 % homology of human A<sub>2B</sub> with human A<sub>1</sub> and A<sub>2A</sub> receptors. The A<sub>3</sub> receptor (317-320 amino acids) was cloned from human, rat, dog, rabbit and sheep.

The A<sub>1</sub> and A<sub>2A</sub> receptor subtypes are proposed to play complementary roles in adenosine's regulation of the energy supply. Adenosine, which is a metabolic product of ATP, diffuses from the cell and acts locally to activate adenosine receptors to decrease the oxygen demand (A<sub>1</sub>) or increase the oxygen supply (A<sub>2A</sub>) and so reinstate the balance of 5 energy supply: demand within the tissue. The actions of both subtypes is to increase the amount of available oxygen to tissue and to protect cells against damage caused by a short term imbalance of oxygen. One of the important functions of endogenous adenosine is preventing damage during traumas such as hypoxia, ischaemia, hypotension and seizure activity.

10 Furthermore, it is known that the binding of the adenosine receptor agonist to mast cells expressing the rat A<sub>3</sub> receptor resulted in increased inositol triphosphate and intracellular calcium concentrations, which potentiated antigen induced secretion of inflammatory mediators. Therefore, the A<sub>3</sub> receptor plays a role in mediating asthmatic attacks and other allergic responses.

15 Adenosine is a neuromodulator, able to modulate many aspects of physiological brain function. Endogenous adenosine, a central link between energy metabolism and neuronal activity, varies according to behavioural state and (patho)physiological conditions. Under conditions of increased demand and decreased availability of energy (such as hypoxia, hypoglycemia, and/or excessive neuronal activity), adenosine provides a 20 powerful protective feedback mechanism. Interacting with adenosine receptors represents a promising target for therapeutic intervention in a number of neurological and psychiatric diseases such as epilepsy, sleep, movement disorders (Parkinson or Huntington's disease), Alzheimer's disease, depression, schizophrenia, or addiction. An increase in neurotransmitter release follows traumas such as hypoxia, ischaemia and seizures. These 25 neurotransmitters are ultimately responsible for neural degeneration and neural death, which causes brain damage or death of the individual. The adenosine A<sub>1</sub> agonists which mimic the central inhibitory effects of adenosine may therefore be useful as neuroprotective agents. Adenosine has been proposed as an endogenous anticonvulsant agent, inhibiting glutamate release from excitatory neurons and inhibiting neuronal firing. 30 Adenosine agonists therefore may be used as antiepileptic agents. Adenosine antagonists stimulate the activity of the CNS and have proven to be effective as cognition enhancers. Selective A<sub>2a</sub> antagonists have therapeutic potential in the treatment of various forms of dementia, for example in Alzheimer's disease, and of neurodegenerative disorders, e.g. stroke. Adenosine A<sub>2a</sub> receptor antagonists modulate the activity of striatal GABAergic 35 neurons and regulate smooth and well-coordinated movements, thus offering a potential therapy for Parkinsonian symptoms. Adenosine is also implicated in a number of physiological processes involved in sedation, hypnosis, schizophrenia, anxiety, pain,

- 4 -

respiration, depression, and drug addiction (amphetamine, cocaine, opioids, ethanol, nicotine, cannabinoids). Drugs acting at adenosine receptors therefore have therapeutic potential as sedatives, muscle relaxants, antipsychotics, anxiolytics, analgesics, respiratory stimulants, antidepressants, and to treat drug abuse. They may also be used in the  
5 treatment of ADHD (attention deficit hyper-activity disorder).

An important role for adenosine in the cardiovascular system is as a cardioprotective agent. Levels of endogenous adenosine increase in response to ischaemia and hypoxia, and protect cardiac tissue during and after trauma (preconditioning). By acting at the A<sub>1</sub> receptor, adenosine A<sub>1</sub> agonists may protect against the injury caused by myocardial  
10 ischemia and reperfusion. The modulating influence of A<sub>2a</sub> receptors on adrenergic function may have implications for a variety of disorders such as coronary artery disease and heart failure. A<sub>2a</sub> antagonists may be of therapeutic benefit in situations in which an enhanced antiadrenergic response is desirable, such as during acute myocardial ischemia.  
15 Selective antagonists at A<sub>2a</sub> receptors may also enhance the effectiveness of adenosine in terminating supraventricular arrhythmias.

Adenosine modulates many aspects of renal function, including renin release, glomerular filtration rate and renal blood flow. Compounds which antagonise the renal affects of adenosine have potential as renal protective agents. Furthermore, adenosine A<sub>3</sub> and/or A<sub>2B</sub> antagonists may be useful in the treatment of asthma and other allergic  
20 responses or and in the treatment of diabetes mellitus and obesity.

Numerous documents describe the current knowledge on adenosine receptors, for example the following publications:

Bioorganic & Medicinal Chemistry, 6, (1998), 619-641,  
Bioorganic & Medicinal Chemistry, 6, (1998), 707-719,  
25 J. Med. Chem., (1998), 41, 2835-2845,  
J. Med. Chem., (1998), 41, 3186-3201,  
J. Med. Chem., (1998), 41, 2126-2133,  
J. Med. Chem., (1999), 42, 706-721,  
J. Med. Chem., (1996), 39, 1164-1171,  
30 Arch. Pharm. Med. Chem., 332, 39-41, (1999),  
Am. J. Physiol., 276, H1113-1116, (1999) or  
Naunyn Schmied, Arch. Pharmacol. 362, 375-381, (2000).

Objects of the present invention are the compounds of formula IA and IB per se, the use of compounds of formula IA and IB and their pharmaceutically acceptable salts for the  
35 manufacture of medicaments for the treatment of diseases, related to the adenosine A<sub>2</sub>

- 5 -

receptor, their manufacture, medicaments based on a compound in accordance with the invention and their production as well as the use of compounds of formula IA and IB in the control or prevention of illnesses based on the modulation of the adenosine system, such as Alzheimer's disease, Parkinson's disease, Huntington's disease, neuroprotection,  
5 schizophrenia, anxiety, pain, respiration deficits, depression, drug addiction, such as amphetamine, cocaine, opioids, ethanol, nicotine, cannabinoids, or against asthma, allergic responses, hypoxia, ischaemia, seizure and substance abuse. Furthermore, compounds of the present invention may be useful as sedatives, muscle relaxants, antipsychotics, antiepileptics, anticonvulsants and cardioprotective agents for disorders such as coronary artery disease and heart failure. The most preferred indications in accordance with the present invention are those, which base on the A<sub>2A</sub> receptor antagonistic activity and which include disorders of the central nervous system, for example the treatment or prevention of Alzheimer's disease, certain depressive disorders, drug addiction, neuroprotection and Parkinson's disease as well as ADHD.

15 As used herein, the term "lower alkyl" denotes a saturated straight- or branched-chain alkyl group containing from 1 to 6 carbon atoms, for example, methyl, ethyl, propyl, isopropyl, n-butyl, i-butyl, 2-butyl, t-butyl and the like. Preferred lower alkyl groups are groups with 1 - 4 carbon atoms.

The term "halogen" denotes chlorine, iodine, fluorine and bromine.

20 The term "lower alkoxy" denotes a group wherein the alkyl residues is as defined above, and which is attached via an oxygen atom.

The term "pharmaceutically acceptable acid addition salts" embraces salts with inorganic and organic acids, such as hydrochloric acid, nitric acid, sulfuric acid, phosphoric acid, citric acid, formic acid, fumaric acid, maleic acid, acetic acid, succinic  
25 acid, tartaric acid, methane-sulfonic acid, p-toluenesulfonic acid and the like.

Preferred compounds of the present application are compounds of formula I, wherein one of R<sup>1</sup>/R<sup>2</sup> is lower alkyl and the other is -(CH<sub>2</sub>)<sub>n</sub>-O-lower alkyl and R<sup>3</sup> is phenyl, optionally substituted by halogen or -(CH<sub>2</sub>)<sub>n</sub>-halogen, for example the following compounds:

30 N-{4-methoxy-7-[(2-methoxy-ethyl)-methyl-amino]-benzothiazol-2-yl}-benzamide, 4-fluoro-N-{4-methoxy-7-[(2-methoxy-ethyl)-methyl-amino]-benzothiazol-2-yl}-benzamide or

4-chloromethyl-N-{4-methoxy-7-[(2-methoxy-ethyl)-methyl-amino]-benzothiazol-2-yl}-benzamide.

Further preferred are compounds, wherein one of R<sup>1</sup>/R<sup>2</sup> is lower alkyl and the other is -(CH<sub>2</sub>)<sub>n</sub>-O-lower alkyl or R<sup>1</sup> and R<sup>2</sup> are together with the N atom the group 2-oxa-5-aza-bicyclo[2.2.1]hept-5-yl and R<sup>3</sup> is pyridinyl, substituted by morpholine, for example the following compounds:

- 5      *N*-{4-methoxy-7-[(2-methoxy-ethyl)-methyl-amino]-benzothiazol-2-yl}-2-morpholin-4-yl-isonicotinamide or
- 10     *N*-[4-methoxy-7-{(1S,4S)-(2-oxa-5-aza-bicyclo[2.2.1]hept-5-yl)}-benzothiazol-2-yl]-2-methyl-isonicotinamide.

A further preferred group of compounds are those, wherein one of R<sup>1</sup>/R<sup>2</sup> is -C(O)-lower alkyl and the other is lower alkyl, -(CH<sub>2</sub>)<sub>n</sub>-O-lower alkyl or benzyl, optionally substituted by lower alkyl and R<sup>3</sup> is phenyl or pyridinyl, which rings are optionally substituted by halogen or lower alkyl, for example the following compounds:

- 15     *N*-{7-[acetyl-(4-methyl-benzyl)-amino]-4-methoxy-benzothiazol-2-yl}-benzamide,
- N*-[7-(acetyl-methyl-amino)-4-methoxy-benzothiazol-2-yl]-4-fluoro-benzamide,
- N*-[7-(acetyl-ethyl-amino)-4-methoxy-benzothiazol-2-yl]-4-fluoro-benzamide,
- N*-[7-(acetyl-benzyl-amino)-4-methoxy-benzothiazol-2-yl]-4-fluoro-benzamide,
- 20     *N*-[7-(acetyl-benzyl-amino)-4-methoxy-benzothiazol-2-yl]-2-bromo-isonicotinamide or
- 25     *N*-{7-[acetyl-(2-methoxy-ethyl)-amino]-4-methoxy-benzothiazol-2-yl}-4-fluoro-benzamide.

Further preferred are compounds, wherein one of R<sup>1</sup>/R<sup>2</sup> is lower alkyl and the other is lower alkyl or benzyl, optionally substituted by lower alkoxy and R<sup>3</sup> is phenyl or pyridinyl, which rings are optionally substituted by morpholinyl, halogen or lower alkyl, for example the following compounds:

- 25     *N*-(7-dimethylamino-4-methoxy-benzothiazol-2-yl)-4-fluoro-benzamide,
- N*-[7-(benzyl-methyl-amino)-4-methoxy-benzothiazol-2-yl]-4-fluoro-benzamide,
- N*-[7-(benzyl-methyl-amino)-4-methoxy-benzothiazol-2-yl]-2-methyl-isonicotinamide,
- 30     4-fluoro-*N*-{4-methoxy-7-[(4-methoxy-benzyl)-methyl-amino]-benzothiazol-2-yl}-benzamide,
- N*-{4-methoxy-7-[(4-methoxy-benzyl)-methyl-amino]-benzothiazol-2-yl}-2-methyl-isonicotinamide,
- N*-[7-(benzyl-methyl-amino)-4-methoxy-benzothiazol-2-yl]-2-bromo-isonicotinamide or
- 35     *N*-[7-(benzyl-methyl-amino)-4-methoxy-benzothiazol-2-yl]-2-morpholin-4-yl-isonicotinamide.

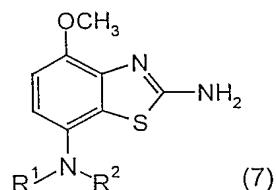
- 7 -

Further preferred are compounds, wherein one of R<sup>1</sup>/R<sup>2</sup> is lower alkyl and the other is -CH<sub>2</sub>-C(O)-N(CH<sub>3</sub>)<sub>2</sub> or tetrahydropyran and R<sup>3</sup> is phenyl or pyridinyl, which rings are optionally substituted by morpholinyl, halogen or lower alkyl, for example the following compounds:

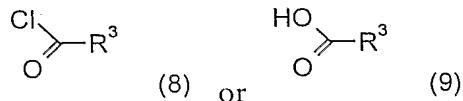
- 5    N-[7-(dimethylcarbamoylmethyl-methyl-amino)-4-methoxy-benzothiazol-2-yl]-4-fluoro-benzamide,
- N-[7-(dimethylcarbamoylmethyl-ethyl-amino)-4-methoxy-benzothiazol-2-yl]-4-fluoro-benzamide,
- 4-fluoro-N-{4-methoxy-7-[methyl-(tetrahydro-pyran-4-yl)-amino]-benzothiazol-2-yl}-
- 10   benzamide or
- N-{4-methoxy-7-[methyl-(tetrahydro-pyran-4-yl)-amino]-benzothiazol-2-yl}-2-morpholin-4-yl-isonicotinamide.

The present compounds of formula I and their pharmaceutically acceptable salts can be prepared by methods known in the art, for example, by processes described below, 15 which process comprises

- a) reacting a compound of formula

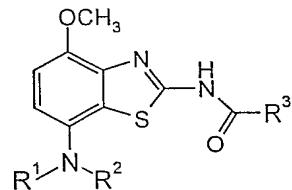


with a compound of formula



20

to a compound of formula



wherein R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> are as defined above, and

- 8 -

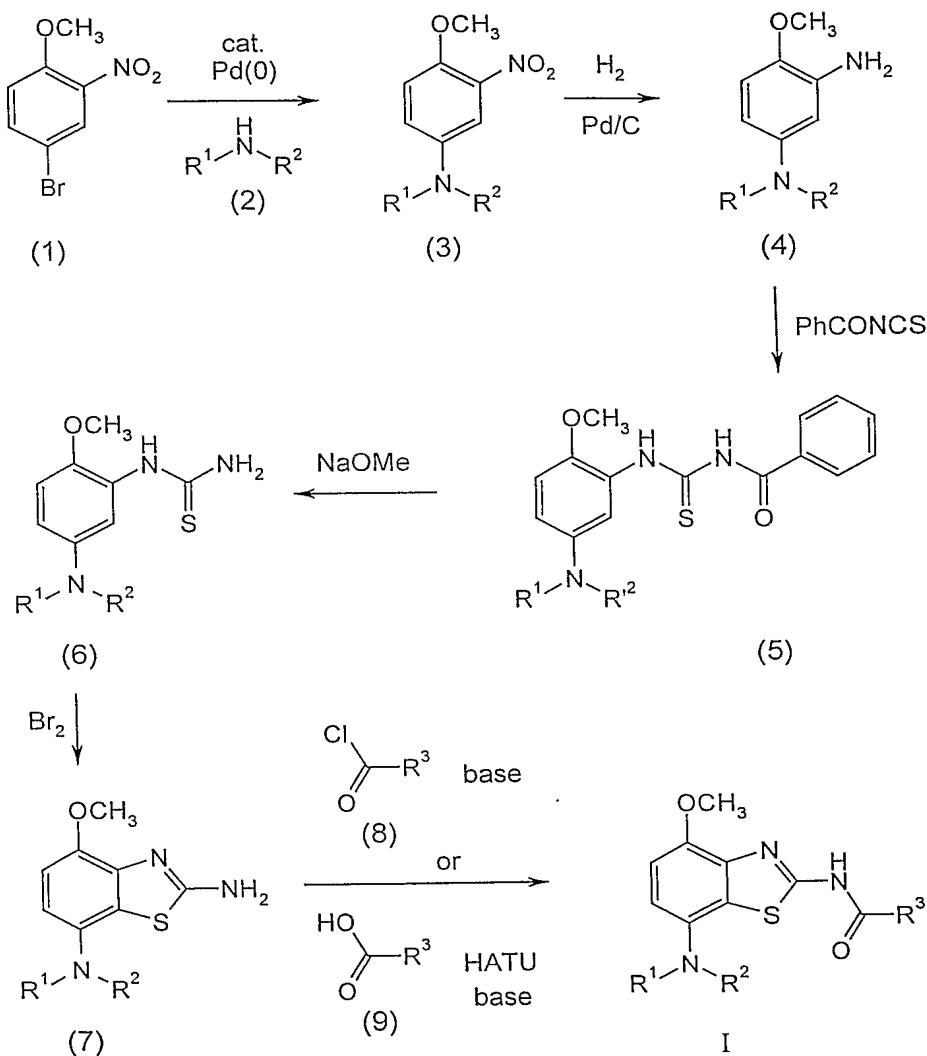
if desired, converting the compounds obtained into pharmaceutically acceptable acid addition salts.

The compounds of formula I may be prepared in accordance with process variant a) and with the following schemes 1 to 4.

##### 5 Preparation of compounds of formula I

One method of preparation of compounds of formula I is from compounds of formula (7), the preparation of which is shown in reaction scheme 1 below.

Scheme 1



- 9 -

where R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> are as defined above.

HATU is O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate.

Preparation of compounds of formula (3)

5 The starting bromoarene compounds of formula (1) may be obtained commercially, for example from Aldrich, or may be prepared according to methods well known in the art. Similarly, the amine compounds of formula (2) may be obtained commercially, for example from Fluka, or may be prepared according to methods well known in the art.

10 The bromoarene compound of formula (1) is reacted with an excess of an amine compound of formula (2), or the corresponding amine hydrochloride salt or hydrobromide salt, in an organic solvent, preferably dioxane, containing a palladium catalyst, preferably palladium(II) acetate, and a catalytic amount of a phosphine ligand, preferably 2-(dicyclohexylphosphino)biphenyl, according to the procedure of Buchwald *et al.* (*J. Am. Chem. Soc.* 1998, 120, 9722). The reaction is carried out in the presence of a base, such as cesium carbonate, potassium phosphate, triethylamine, or a combination of these. The reaction is carried out at elevated temperature, preferably about 80-100 °C, for about 2-24 hours, preferably about 16 hours. The product of formula (3) is isolated by conventional means, and preferably purified by means of chromatography or recrystallisation.

20 Preparation of compounds of formula (4)

Compounds of formula (4) may be prepared by hydrogenation of compounds of formula (3) in the presence of a hydrogenation catalyst, preferably 10 % palladium on charcoal. These reactions may be carried out in a variety of organic solvents, such as methanol, ethanol, dichloromethane or tetrahydrofuran, preferably a mixture of methanol and dichloromethane, at room temperature and at a pressure of one atmosphere or above, preferably at one atmosphere, for 2-24 hours, preferably about 16 hours. The product of formula (4) is isolated by conventional means, and preferably purified by means of chromatography or recrystallisation.

Preparation of compounds of formula (5)

30 One method of preparation of compounds of formula (5) involves treatment of a compound of formula (4) with a slight excess of benzoyl isothiocyanate in acetone at a temperature between room temperature and reflux, preferably at room temperature, for 30-60 minutes, preferably 30 minutes. The product of formula (5) is isolated by

- 10 -

conventional means, and preferably purified by means of chromatography or recrystallisation.

Preparation of compounds of formula (6)

5 A compound of formula (5) is treated with a sub-stoichiometric amount of an alkali metal alcoholate in the corresponding alcohol solvent, preferably sodium methylate in methanol. The reaction is carried out at room temperature for about 0.5-2 hours, preferably about 1 hour. The product of formula (6) is isolated by conventional means, and preferably purified by means of chromatography or recrystallisation.

Preparation of compounds of formula (7)

10 One method of preparation of compounds of formula (7) is by treatment of a compound of formula (6) with a stoichiometric equivalent of bromine in a halogenated organic solvent, preferably chloroform. The reaction is carried out at elevated temperature, preferably at the reflux temperature of the solvent, for about 12-18 hours, preferably about 16 hours. The product of formula (7) is isolated by conventional means, and preferably purified by means of chromatography or recrystallisation.

Preparation of compounds of formula I

One method of preparation of compounds of formula I is by treatment of a compound of formula (7) with a slight excess of an appropriate acyl chloride of formula (8), which may be commercially available or may be prepared by methods well known in the art. The  
20 reaction is carried out in a non-protic organic solvent, preferably a mixture of dichloromethane and tetrahydrofuran, containing a base, preferably *N*-ethyldiisopropylamine or triethylamine, at room temperature for 2-24 hours, preferably 24 hours. The product of formula I is isolated by conventional means, and preferably purified by means of chromatography or recrystallisation.

25 Alternative preparation of compounds of formula I

An alternative method of preparation of compounds of formula I involves treatment of an appropriate carboxylic acid of formula (9) with a stoichiometric equivalent of a peptide-coupling reagent, preferably *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HATU), in an ethereal solvent, preferably tetrahydrofuran,  
30 containing a base, preferably *N*-ethyldiisopropylamine, at room temperature for 30-90 minutes, preferably 1 hour. This mixture is then treated with a compound of formula (7) in a solvent mixture, preferably a mixture of tetrahydrofuran, dioxane and *N,N*-dimethylformamide, at room temperature for 16-24 hours, preferably 16 hours. The

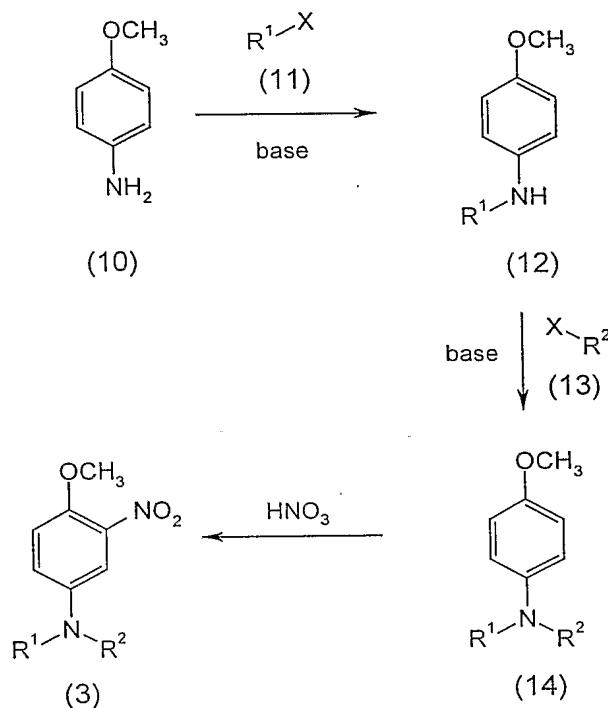
- 11 -

product of formula I is isolated by conventional means, and preferably purified by means of chromatography or recrystallisation.

Alternative preparation of compounds of formula (3)

An alternative method of preparation of compounds of formula (3) is from intermediates 5 of formula (14), the preparation of which is shown in reaction scheme 2 below.

Scheme 2



10 where R<sup>1</sup> and R<sup>2</sup> are as defined above, and X is Br or I.

Preparation of compounds of formula (12)

The starting aryl amines of formula (10) may be obtained commercially, for example from Fluka, or may be prepared according to methods well known in the art. Similarly, the starting alkyl iodide or alkyl bromide compounds of formula (11) may be obtained 15 commercially, for example from Fluka, or may be prepared according to methods well known in the art.

The aryl amine compound of formula (10) is reacted with a stoichiometric equivalent of an alkyl iodide or alkyl bromide compound of formula (11) in an organic solvent, preferably N,N-dimethylformamide or acetonitrile, containing a base, preferably potassium carbonate 20 or N,N-diisopropylethylamine. The reaction is carried out at a temperature between room

- 12 -

temperature and the reflux temperature of the solvent, for about 1-48 hours, preferably about 16 hours. The product of formula (12) is isolated by conventional means, and preferably purified by means of chromatography or recrystallisation.

Preparation of compounds of formula (14)

5. The starting alkyl iodide or alkyl bromide compounds of formula (13) may be obtained commercially, for example from Fluka, or may be prepared according to methods well known in the art.

The aryl amine compound of formula (12) is reacted with a stoichiometric equivalent of an alkyl iodide or alkyl bromide compound of formula (13) in an organic solvent, preferably 10 *N,N*-dimethylformamide or acetonitrile, containing a base, preferably potassium carbonate or *N,N*-diisopropylethylamine. The reaction is carried out at a temperature between room temperature and the reflux temperature of the solvent, for about 1-48 hours, preferably about 16 hours. The product of formula (14) is isolated by conventional means, and preferably purified by means of chromatography or recrystallisation.

15      Preparation of compounds of formula (3)

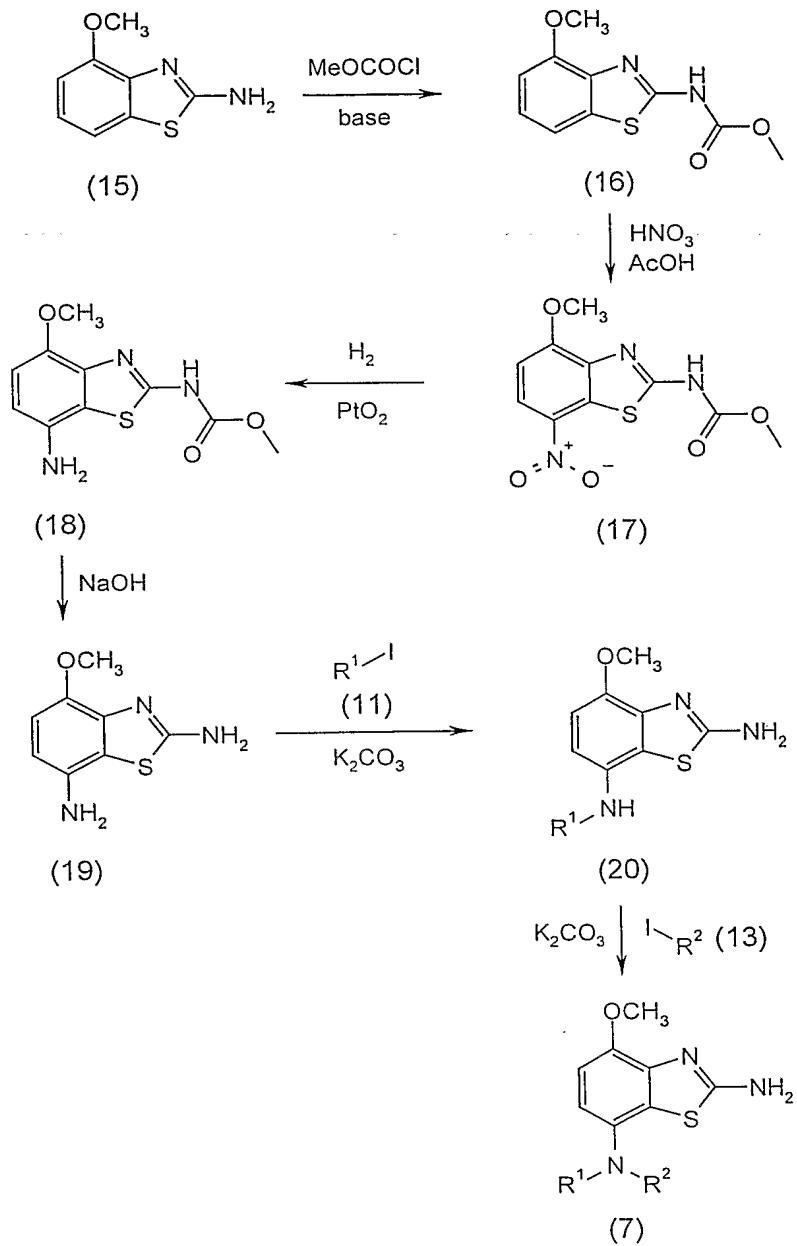
The compound of formula (14) is reacted with a nitrating agent, such as 65 % nitric acid or potassium nitrate in 98% sulfuric acid, in an acidic solvent, such as acetic acid or 98 % sulfuric acid. The reaction is carried out at a temperature between 20 °C and 80 °C, for about 2-16 hours. The product of formula (3) is isolated by conventional means, and 20 preferably purified by means of chromatography or recrystallisation.

Alternative Preparation of compounds of formula (7)

An alternative method of preparation of compounds of formula (7) is from intermediates of formula (20), the preparation of which is shown in reaction scheme 3 below.

- 13 -

Scheme 3



wherein R<sup>1</sup> and R<sup>2</sup> are as defined above.

Preparation of compounds of formula (16)

- 5 The starting 2-amino-benzothiazole compounds of formula (15) may be obtained commercially, for example from Aldrich, or may be prepared according to methods well known in the art.

The 2-amino-benzothiazole compound of formula (15) is reacted with a stoichiometric equivalent of methyl chloroformate in an organic solvent, preferably dichloromethane,

- 14 -

containing a base, preferably pyridine. The reaction is carried out at a temperature between 0 °C and room temperature, preferably at 0 °C, for about 1-2 hours, preferably about 1 hour. The product of formula (16) is isolated by conventional means, and preferably purified by means of chromatography or recrystallisation.

5      Preparation of compounds of formula (17)

The compound of formula (16) is reacted with a nitrating agent, preferably 65 % nitric acid, in an acidic solvent, preferably acetic acid. The reaction is carried out at an elevated temperature, preferably about 70 °C, for about 2-16 hours, preferably 4 hours. The product of formula (17) is isolated by conventional means, and preferably purified by means of 10 chromatography or recrystallisation.

Preparation of compounds of formula (18)

Compounds of formula (18) may be prepared by hydrogenation of compounds of formula (17) in the presence of a hydrogenation catalyst, preferably platinum(IV) oxide. These reactions may be carried out in a variety of organic solvents, such as methanol, ethanol, 15 dichloromethane or tetrahydrofuran, preferably a mixture of methanol and dichloromethane, at room temperature and at a pressure of one atmosphere or above, preferably at one atmosphere, for 2-24 hours, preferably about 16 hours. The product of formula (18) is isolated by conventional means, and preferably purified by means of chromatography or recrystallisation.

20      Preparation of compounds of formula (19)

One method of preparation of compounds of formula (19) is by treatment of a compound of formula (18) with an excess of sodium hydroxide or potassium hydroxide in an aqueous solvent, preferably aqueous ethylene glycol. The reaction is carried out at elevated temperature, preferably about 100 °C, for about 1-16 hours, preferably about 6 hours. The 25 product of formula (19) is isolated by conventional means, and preferably purified by means of chromatography or recrystallisation.

Preparation of compounds of formula (20)

The starting alkyl iodides of formula (11) may be obtained commercially, for example from Fluka, or may be prepared according to methods well known in the art.

30      The compound of formula (19) is reacted with a stoichiometric equivalent of an alkyl iodide compound of formula (11) in an organic solvent, preferably *N,N*-dimethylformamide, containing a base, preferably potassium carbonate. The reaction is carried out at a temperature between room temperature and the reflux temperature of the

- 15 -

solvent, for about 1-48 hours, preferably about 16 hours. The product of formula (20) is isolated by conventional means, and preferably purified by means of chromatography or recrystallisation.

## Preparation of compounds of formula (7)

- 5 The starting alkyl iodides of formula (13) may be obtained commercially, for example from Fluka, or may be prepared according to methods well known in the art.

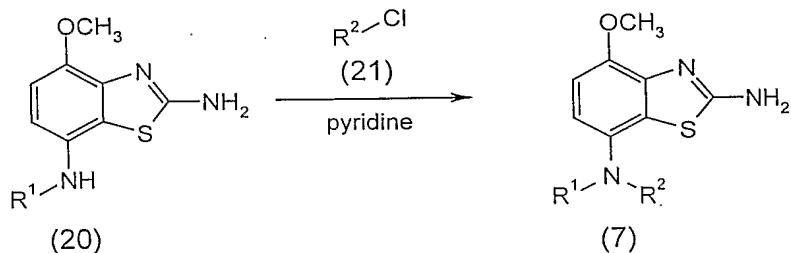
The compound of formula (20) is reacted with a stoichiometric equivalent of an alkyl iodide compound of formula (13) in an organic solvent, preferably *N,N*-dimethylformamide, containing a base, preferably potassium carbonate. The reaction is carried out at a temperature between room temperature and the reflux temperature of the solvent, for about 1-48 hours, preferably about 16 hours. The product of formula (7) is isolated by conventional means, and preferably purified by means of chromatography or recrystallisation.

Alternative Preparation of compounds of formula (7) where R<sup>2</sup> is -C(O)-lower alkyl, -C(O)-C<sub>5,6</sub>-cycloalkyl, or -C(O)-tetrahydropyran-2,3 or 4-yl.

An alternative method of preparation of compounds of formula (7) from intermediates of formula (20) in the case where R<sup>2</sup> contains an acyl group, i.e where R<sup>2</sup> is -C(O)-lower alkyl, -C(O)-C<sub>5,6</sub>-cycloalkyl, or -C(O)-tetrahydropyran-2,3 or 4-yl, is shown in reaction scheme 4 below.

20

Scheme 4



wherein R<sup>1</sup> is as defined above and R<sup>2</sup> is -C(O)-lower alkyl, -C(O)-C<sub>5,6</sub>-cycloalkyl, -C(O)-tetrahydropyran-2,3 or 4-yl.

The starting acyl chlorides of formula (21) may be obtained commercially, for example from Fluka, or may be prepared according to methods well known in the art.

The compound of formula (20) is reacted with a stoichiometric equivalent of an acyl chloride compound of formula (21) in an organic solvent, preferably a mixture of

- 16 -

dichloromethane and tetrahydrofuran, containing a base, preferably pyridine. The reaction is carried out at a temperature between 0 °C and room temperature, preferably at 0 °C, for about 1-16 hours, preferably about 3 hours. The product of formula (7) is isolated by conventional means, and preferably purified by means of chromatography or  
5 recrystallisation.

Isolation and purification of the compounds

Isolation and purification of the compounds and intermediates described herein can be effected, if desired, by any suitable separation or purification procedure such as, for example, filtration, extraction, crystallization, column chromatography, thin-layer  
10 chromatography, thick-layer chromatography, preparative low or high-pressure liquid chromatography or a combination of these procedures. Specific illustrations of suitable separation and isolation procedures can be had by reference to the Preparations and Examples herein below. However, other equivalent separation or isolation procedures could, of course, also be used.

15 Salts of compounds of Formula I

The compounds of formula I may be basic, for example in cases where the residue R contains a basic group such as an aliphatic or aromatic amine moiety. In such cases the compounds of formula I may be converted to a corresponding acid addition salt.

The conversion is accomplished by treatment with at least a stoichiometric amount of an  
20 appropriate acid, such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, and organic acids such as acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, malic acid, malonic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like. Typically, the  
25 free base is dissolved in an inert organic solvent such as diethyl ether, ethyl acetate, chloroform, ethanol or methanol and the like, and the acid added in a similar solvent. The temperature is maintained between 0 °C and 50 °C. The resulting salt precipitates spontaneously or may be brought out of solution with a less polar solvent.

The acid addition salts of the basic compounds of formula I may be converted to the  
30 corresponding free bases by treatment with at least a stoichiometric equivalent of a suitable base such as sodium or potassium hydroxide, potassium carbonate, sodium bicarbonate, ammonia, and the like.

The compounds of formula I and their pharmaceutically usable addition salts possess valuable pharmacological properties. Specifically, it has been found that the compounds of

- 17 -

the present invention are adenosine receptor ligands and possess a high affinity towards the adenosine A<sub>2A</sub> receptor.

The compounds were investigated in accordance with the test given hereinafter.

Human adenosine A<sub>2A</sub> receptor

- 5    The human adenosine A<sub>2A</sub> receptor was recombinantly expressed in chinese hamster ovary (CHO) cells using the semliki forest virus expression system. Cells were harvested, washed twice by centrifugation, homogenised and again washed by centrifugation. The final washed membrane pellet was suspended in a Tris (50 mM) buffer containing 120 mM NaCl, 5 mM KCl, 2 mM CaCl<sub>2</sub> and 10 mM MgCl<sub>2</sub> (pH 7.4) (buffer A). The [3H]-SCH-  
 10   58261 (Dionisotti et al., 1997, Br J Pharmacol 121, 353; 1nM) binding assay was carried out in 96-well plates in the presence of 2.5 µg of membrane protein, 0.5 mg of Ysi-poly-l-lysine SPA beads and 0.1 U adenosine deaminase in a final volume of 200 µl of buffer A. Non-specific binding was defined using xanthine amine congener (XAC; 2 µM). Compounds were tested at 10 concentrations from 10 µM - 0.3 nM. All assays were conducted in  
 15   duplicate and repeated at least two times. Assay plates were incubated for 1hour at room temperature before centrifugation and then bound ligand determined using a Packard Topcount scintillation counter. IC<sub>50</sub> values were calculated using a non-linear curve fitting program and Ki values calculated using the Cheng-Prussoff equation.

The preferred compounds show a pKi > 7.2.

Example No.	hA2 (pKi)	Example No.	hA2 (pKi)
1	7.28	20	7.21
2	7.42	21	8.00
3	7.43	24	7.97
6	7.28	25	7.28
10	7.94	26	7.75
12	7.13	28	7.31
14	7.41	30	7.58
15	7.21	32	7.48

16	7.81	35	7.96
17	7.22	37	7.25
19	7.88	38	7.33

The compounds of formula I and the pharmaceutically acceptable salts of the compounds of formula I can be used as medicaments, e.g. in the form of pharmaceutical preparations. The pharmaceutical preparations can be administered orally, e.g. in the form 5 of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions. The administration can, however, also be effected rectally, e.g. in the form of suppositories, parenterally, e.g. in the form of injection solutions.

The compounds of formula I can be processed with pharmaceutically inert, inorganic or organic carriers for the production of pharmaceutical preparations. Lactose, corn starch 10 or derivatives thereof, talc, stearic acids or its salts and the like can be used, for example, as such carriers for tablets, coated tablets, dragées and hard gelatine capsules. Suitable carriers for soft gelatine capsules are, for example, vegetable oils, waxes, fats, semi-solid and liquid polyols and the like. Depending on the nature of the active substance no carriers are, however, usually required in the case of soft gelatine capsules. Suitable carriers for the 15 production of solutions and syrups are, for example, water, polyols, glycerol, vegetable oil and the like. Suitable carriers for suppositories are, for example, natural or hardened oils, waxes, fats, semi-liquid or liquid polyols and the like.

The pharmaceutical preparations can, moreover, contain preservatives, solubilizers, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for varying 20 the osmotic pressure, buffers, masking agents or antioxidants. They can also contain still other therapeutically valuable substances.

Medicaments containing a compound of formula I or a pharmaceutically acceptable salt thereof and a therapeutically inert carrier are also an object of the present invention, as is a process for their production, which comprises bringing one or more compounds of 25 formula I and/or pharmaceutically acceptable acid addition salts and, if desired, one or more other therapeutically valuable substances into a galenical administration form together with one or more therapeutically inert carriers.

In accordance with the invention compounds of formula I as well as their pharmaceutically acceptable salts are useful in the control or prevention of illnesses based

- 19 -

on the adenosine receptor antagonistic activity, such as Alzheimer's disease, Parkinson's disease, neuroprotection, schizophrenia, anxiety, pain, respiration deficits, depression, asthma, allergic responses, hypoxia, ischaemia, seizure and substance abuse. Furthermore, compounds of the present invention may be useful as sedatives, muscle relaxants, 5 antipsychotics, antiepileptics, anticonvulsants and cardioprotective agents and for the production of corresponding medicaments.

The most preferred indications in accordance with the present invention are those, which include disorders of the central nervous system, for example the treatment or prevention of certain depressive disorders, neuroprotection and Parkinson's disease.

10 The dosage can vary within wide limits and will, of course, have to be adjusted to the individual requirements in each particular case. In the case of oral administration the dosage for adults can vary from about 0.01 mg to about 1000 mg per day of a compound of general formula I or of the corresponding amount of a pharmaceutically acceptable salt thereof. The daily dosage may be administered as single dose or in divided doses and, in 15 addition, the upper limit can also be exceeded when this is found to be indicated.

#### Tablet Formulation (Wet Granulation)

<u>Item</u>	<u>Ingredients</u>	<u>mg/tablet</u>			
		5 mg	25 mg	100 mg	500 mg
1.	Compound of formula I	5	25	100	500
20	2. Lactose Anhydrous DTG	125	105	30	150
3.	Sta-Rx 1500	6	6	6	30
4.	Microcrystalline Cellulose	30	30	30	150
5.	Magnesium Stearate	1	1	1	1
	Total	167	167	167	831

#### 25 Manufacturing Procedure

1. Mix items 1, 2, 3 and 4 and granulate with purified water.
2. Dry the granules at 50°C.
3. Pass the granules through suitable milling equipment.
4. Add item 5 and mix for three minutes; compress on a suitable press.

- 20 -

Capsule Formulation

<u>Item</u>	<u>Ingredients</u>	<u>mg/capsule</u>			
		5 mg	25 mg	100 mg	500 mg
1.	Compound of formula I	5	25	100	500
5	2. Hydrous Lactose	159	123	148	---
	3. Corn Starch	25	35	40	70
	4. Talc	10	15	10	25
	5. Magnesium Stearate	1	2	2	5
	Total	200	200	300	600

10 Manufacturing Procedure

1. Mix items 1, 2 and 3 in a suitable mixer for 30 minutes.
2. Add items 4 and 5 and mix for 3 minutes.
3. Fill into a suitable capsule.

Example 1

15 N-{4-Methoxy-7-[(2-methoxy-ethyl)-methyl-amino]-benzothiazol-2-yl}-benzamide

a) (2-Methoxy-ethyl)-(4-methoxy-phenyl)-methyl-amine

To a stirred solution of 1.00 g (7.29 mmol) *N*-methyl-*p*-anisidine in 15 ml acetonitrile at 0 °C were added dropwise 1.36 ml (8.02 mmol) *N*-ethyldiisopropylamine and 1.01 g (7.29 mmol) 2-bromoethyl methyl ether. The mixture was heated at 80 °C for 2 days and then 20 concentrated *in vacuo*. Flash chromatography (1/9 ethyl acetate/hexane) afforded 1.20 g (84 %) (2-methoxy-ethyl)-(4-methoxy-phenyl)-methyl-amine as an orange oil. ES-MS m/e (%): 196 ( $M+H^+$ , 100).

b) (2-Methoxy-ethyl)-(4-methoxy-3-nitro-phenyl)-methyl-amine

To a stirred solution of 600 mg (3.07 mmol) (2-methoxy-ethyl)-(4-methoxy-phenyl)-methyl-amine in 1.3 ml concentrated sulfuric acid at room temperature was added 222 mg (3.69 mmol) urea. After stirring for 1 h at room temperature, a solution of 342 mg (3.38 mmol) potassium nitrate in 0.6 ml concentrated sulfuric acid was added dropwise and stirring continued for a further 16 h. The mixture was then poured onto water and extracted five times with dichloromethane. The combined organic phases were dried over 30 sodium sulfate and concentrated *in vacuo*. Flash chromatography (1/9 ethyl

- 21 -

acetate/hexane) afforded 260 mg (35 %) (2-methoxy-ethyl)-(4-methoxy-3-nitro-phenyl)-methyl-amine as an orange oil. ES-MS m/e (%): 241 (M+H<sup>+</sup>, 100).

c) 4-Methoxy-N1-(2-methoxy-ethyl)-N1-methyl-benzene-1,3-diamine

To a stirred solution of 2.50 g (10.4 mmol) (2-methoxy-ethyl)-(4-methoxy-3-nitro-phenyl)-methyl-amine in 100 ml methanol was added a spatula end of 10 % palladium on charcoal and the mixture was then stirred for 16 hours at room temperature under an atmosphere of hydrogen. The mixture was then filtered and the filtrate concentrated *in vacuo* to afford 1.90 g (87 %) 4-methoxy-N1-(2-methoxy-ethyl)-N1-methyl-benzene-1,3-diamine as an off-white crystalline solid. ES-MS m/e (%): 211 (M+H<sup>+</sup>, 100).

10 d) 1-Benzoyl-3-{2-methoxy-5-[(2-methoxy-ethyl)-methyl-amino]-phenyl}-thiourea

To a stirred solution of 1.89 g (8.99 mmol) 4-methoxy-N1-(2-methoxy-ethyl)-N1-methyl-benzene-1,3-diamine in 60 ml acetone was added dropwise a solution of 1.38 ml (10.3 mmol) benzoyl isothiocyanate in 30 ml acetone and stirring continued at room temperature for 30 minutes. The mixture was then concentrated *in vacuo*. Trituration in ether afforded 2.05 g (61 %) 1-benzoyl-3-{2-methoxy-5-[(2-methoxy-ethyl)-methyl-amino]-phenyl}-thiourea as a yellow solid. ES-MS m/e (%): 374 (M+H<sup>+</sup>, 100).

e) N-{4-Methoxy-7-[(2-methoxy-ethyl)-methyl-amino]-benzothiazol-2-yl}-benzamide

To a stirred solution of 430 mg (1.15 mmol) 1-benzoyl-3-{2-methoxy-5-[(2-methoxy-ethyl)-methyl-amino]-phenyl}-thiourea in 8 ml chloroform was added dropwise 0.059 ml (1.15 mmol) bromine and the reaction mixture heated at reflux for 18 hours. The mixture was then cooled to room temperature, poured slowly onto water and extracted three times with ethyl acetate. The combined organic phases were dried over sodium sulfate and concentrated *in vacuo*. Flash chromatography (1/4 ethyl acetate/hexane) afforded 120 mg (28 %) N-{4-methoxy-7-[(2-methoxy-ethyl)-methyl-amino]-benzothiazol-2-yl}-benzamide as a yellow solid. ES-MS m/e (%): 394 (M+Na<sup>+</sup>, 14), 372 (M+H<sup>+</sup>, 100).

Example 2

4-Fluoro-N-{4-methoxy-7-[(2-methoxy-ethyl)-methyl-amino]-benzothiazol-2-yl}-benzamide

a) {2-Methoxy-5-[(2-methoxy-ethyl)-methyl-amino]-phenyl}-thiourea

30 To a stirred suspension of 2.00 g (5.36 mmol) 1-benzoyl-3-{2-methoxy-5-[(2-methoxy-ethyl)-methyl-amino]-phenyl}-thiourea in 13 ml methanol was added dropwise 0.15 ml (0.80 mmol) 5.4 M sodium methylate solution and stirring continued for 1 h at room

- 22 -

temperature. The mixture was then poured onto water and extracted three times with ethyl acetate. The combined organic phases were dried over sodium sulfate and concentrated *in vacuo*. Flash chromatography (ethyl acetate) afforded 1.40 g (97 %) {2-methoxy-5-[(2-methoxy-ethyl)-methyl-amino]-phenyl}-thiourea as an amber oil. ES-MS m/e (%): 270 (M+H<sup>+</sup>, 100).

5 b) 4-Methoxy-N7-(2-methoxy-ethyl)-N7-methyl-benzothiazole-2,7-diamine

To a stirred solution of 1.40 g (5.20 mmol) {2-methoxy-5-[(2-methoxy-ethyl)-methyl-amino]-phenyl}-thiourea in 35 ml chloroform was added dropwise 0.27 ml (5.27 mmol) bromine and the reaction mixture heated at reflux for 18 hours. The mixture was then 10 cooled to room temperature, poured slowly onto sodium bicarbonate solution and extracted three times with ethyl acetate. The combined organic phases were dried over sodium sulfate and concentrated *in vacuo*. Flash chromatography (ethyl acetate) afforded 984 mg (71 %) 4-methoxy-N7-(2-methoxy-ethyl)-N7-methyl-benzothiazole-2,7-diamine as an orange crystalline solid. ES-MS m/e (%): 268 (M+H<sup>+</sup>, 100).

15 c) 4-Fluoro-N-{4-methoxy-7-[(2-methoxy-ethyl)-methyl-amino]-benzothiazol-2-yl}-benzamide

To a stirred solution of 79 mg (0.56 mmol) 4-fluoro-benzoic acid in 10 ml THF were added 235 mg (0.62 mmol) HATU and 0.11 ml (0.62 mmol) N-ethyldiisopropylamine and stirring continued at room temperature for 1 h. A solution of 150 mg (0.56 mmol) 4-methoxy-N7-(2-methoxy-ethyl)-N7-methyl-benzothiazole-2,7-diamine in 5 ml dioxane and 1 ml DMF was then added and stirring continued at room temperature for 16 h. The reaction mixture was then poured into 100 ml 1 M hydrochloric acid and extracted three times with dichloromethane. The combined organic phases were dried over sodium sulfate and concentrated *in vacuo*. Flash chromatography (1/4 – 1/1 ethyl acetate/hexane) followed 20 by trituration in hexane afforded 55 mg (25 %) 4-fluoro-N-{4-methoxy-7-[(2-methoxy-ethyl)-methyl-amino]-benzothiazol-2-yl}-benzamide as an off-white crystalline solid. ES-MS m/e (%): 390 (M+H<sup>+</sup>, 100).

25 Example 3

30 4-Chloromethyl-N-{4-methoxy-7-[(2-methoxy-ethyl)-methyl-amino]-benzothiazol-2-yl}-benzamide

To a stirred solution of 300 mg (1.12 mmol) 4-methoxy-N7-(2-methoxy-ethyl)-N7-methyl-benzothiazole-2,7-diamine and 1.12 ml (6.56 mmol) N-ethyldiisopropylamine in 10 ml THF at room temperature was added dropwise a solution of 257 mg (1.36 mmol) 4-(chloromethyl)-benzoyl chloride in 3 ml dichloromethane and stirring continued at room

- 23 -

temperature for 16 h. The reaction mixture was then concentrated *in vacuo*. Flash chromatography (1/1 ethyl acetate/hexane) followed by trituration in ether and hexane afforded 200 mg (42 %) 4-chloromethyl-N-[4-methoxy-7-[(2-methoxy-ethyl)-methyl-amino]-benzothiazol-2-yl]-benzamide as a light yellow crystalline solid. ES-MS m/e (%):  
5 422 ( $M\{^{37}\text{Cl}\} + \text{H}^+$ , 32), 420 ( $M\{^{35}\text{Cl}\} + \text{H}^+$ , 100).

Analogously to Example 2 there were obtained:

#### Example 4

*N*-{4-Methoxy-7-[(2-methoxy-ethyl)-methyl-amino]-benzothiazol-2-yl}-2-methylisonicotinamide

10 From 2-methyl-isonicotinic acid hydrochloride, HATU and *N*-diethylisopropylamine in THF, then treatment with 4-methoxy-*N*7-(2-methoxy-ethyl)-*N*7-methyl-benzothiazole-2,7-diamine in dioxane and DMF. ES-MS m/e (%): 387 ( $M + \text{H}^+$ , 100).

#### Example 5

15 2-Bromo-*N*-{4-methoxy-7-[(2-methoxy-ethyl)-methyl-amino]-benzothiazol-2-yl}-isonicotinamide

From 2-bromo-isonicotinic acid, HATU and *N*-diethylisopropylamine in THF, then treatment with 4-methoxy-*N*7-(2-methoxy-ethyl)-*N*7-methyl-benzothiazole-2,7-diamine in dioxane and DMF. ES-MS m/e (%): 453 ( $M\{^{81}\text{Br}\} + \text{H}^+$ , 100), 451 ( $M\{^{79}\text{Br}\} + \text{H}^+$ , 71).

20 Example 6

*N*-{4-Methoxy-7-[(2-methoxy-ethyl)-methyl-amino]-benzothiazol-2-yl}-2-morpholin-4-yl-isonicotinamide

A stirred suspension of 200 mg (0.44 mmol) 2-bromo-*N*-{4-methoxy-7-[(2-methoxy-ethyl)-methyl-amino]-benzothiazol-2-yl}-isonicotinamide, 0.38 ml (4.43 mmol)  
25 morpholine and 289 mg (0.89 mmol) cesium carbonate in 5 ml *N*-methylpyrrolidone in a thick-walled glass pressure tube fitted with a teflon cap was heated at 140 °C for 24 h. The reaction mixture was then cooled to room temperature and poured onto water. The mixture was extracted three times with ethyl acetate, and the combined organic phases were dried over sodium sulfate and concentrated *in vacuo*. Flash chromatography (ethyl acetate) followed by trituration in ether afforded 100 mg (49 %) *N*-{4-methoxy-7-[(2-methoxy-ethyl)-methyl-amino]-benzothiazol-2-yl}-2-morpholin-4-yl-isonicotinamide as a light yellow crystalline solid. ES-MS m/e (%): 458 ( $M + \text{H}^+$ , 100).  
30

- 24 -

**Example 7**

*N*-[4-Methoxy-7- $\{(1S,4S)$ -(2-oxa-5-aza-bicyclo[2.2.1]hept-5-yl)}-benzothiazol-2-yl]-2-methyl-isonicotinamide

a) (1S,4S)-5-(4-Methoxy-3-nitro-phenyl)-2-oxa-5-aza-bicyclo[2.2.1]heptane

5 To a stirred solution of 7.34 g (31.0 mmol) 4-bromo-2-nitro-anisole in 125 ml dioxane were added 5.25 g (37.2 mmol) (1S,4S)-(+)-2-aza-5-oxabicyclo[2.2.1] heptane hydrochloride, 1.109 g (3.10 mmol) 2-(dicyclohexylphosphino)biphenyl, 14.2 g (43.4 mmol) cesium carbonate, 696 mg (3.10 mmol) palladium(II) acetate and 5.65 ml (40.3 mmol) triethylamine. The mixture was heated at reflux for 24 h and then poured onto 10 water and extracted three times with ethyl acetate. The combined organic phases were dried over sodium sulfate and concentrated *in vacuo*. Flash chromatography (1/99 methanol/dichloromethane) afforded 5.10 g (66 %) (1S,4S)-5-(4-methoxy-3-nitro-phenyl)-2-oxa-5-aza-bicyclo[2.2.1]heptane as an orange oil. ES-MS m/e (%): 251 (M+H<sup>+</sup>, 100).

b) 2-Methoxy-5- $\{(1S,4S)$ -(2-oxa-5-aza-bicyclo[2.2.1]hept-5-yl)}-phenylamine

To a stirred solution of 5.01 g (20.0 mmol) (1S,4S)-5-(4-methoxy-3-nitro-phenyl)-2-oxa-5-aza-bicyclo[2.2.1]heptane in 375 ml methanol and 62.5 ml dichloromethane was added 500 mg 10 % palladium on charcoal and the mixture was then stirred for 3.5 hours at room temperature under an atmosphere of hydrogen. The mixture was then filtered and the 20 filtrate concentrated *in vacuo* to afford 4.30 g (98 %) 2-methoxy-5- $\{(1S,4S)$ -(2-oxa-5-aza-bicyclo[2.2.1]hept-5-yl)}-phenylamine as a brown crystalline solid. ES-MS m/e (%): 221 (M+H<sup>+</sup>, 100).

c) 1-Benzoyl-3-[2-methoxy-5- $\{(1S,4S)$ -(2-oxa-5-aza-bicyclo[2.2.1]hept-5-yl)}-phenyl]-thiourea

25 To a stirred solution of 4.20 g (19.1 mmol) 2-methoxy-5- $\{(1S,4S)$ -(2-oxa-5-aza-bicyclo[2.2.1]hept-5-yl)}-phenylamine in 200 ml acetone was added dropwise 2.88 ml (21.0 mmol) benzoyl isothiocyanate and stirring continued for 1 h at room temperature. The mixture was then concentrated *in vacuo* to afford 7.30 g (100 %) 1-benzoyl-3-[2-methoxy-5- $\{(1S,4S)$ -(2-oxa-5-aza-bicyclo[2.2.1]hept-5-yl)}-phenyl]-thiourea as a yellow 30 solid. ES-MS m/e (%): 406 (M+Na<sup>+</sup>, 13), 384 (M+H<sup>+</sup>, 100).

d) [2-Methoxy-5- $\{(1S,4S)$ -(2-oxa-5-aza-bicyclo[2.2.1]hept-5-yl)}-phenyl]-thiourea

To a stirred suspension of 7.25 g (18.9 mmol) 1-benzoyl-3-[2-methoxy-5- $\{(1S,4S)$ -(2-oxa-5-aza-bicyclo[2.2.1]hept-5-yl)}-phenyl]-thiourea in 350 ml methanol was added dropwise

- 25 -

7.02 ml (37.8 mmol) 5.4 M sodium methylate solution and stirring continued for 1 h at room temperature. The resulting crystals were collected by filtration to afford 3.42 g (65 %) [2-methoxy-5- $\{(1S,4S)$ -(2-oxa-5-aza-bicyclo[2.2.1]hept-5-yl)}-phenyl]-thiourea as a beige solid. ES-MS m/e (%): 302 (M+Na<sup>+</sup>, 20), 281 (M+H<sup>+</sup>, 100).

5    e) 4-Methoxy-7- $\{(1S,4S)$ -(2-oxa-5-aza-bicyclo[2.2.1]hept-5-yl)}-benzothiazol-2-ylamine

To a stirred solution of 279 mg (1.00 mmol) [2-methoxy-5- $\{(1S,4S)$ -(2-oxa-5-aza-bicyclo[2.2.1]hept-5-yl)}-phenyl]-thiourea in 8 ml chloroform at room temperature was added dropwise 0.051 ml (1.00 mmol) bromine and the mixture heated at reflux for 24 h. The mixture was then concentrated *in vacuo* and the residue suspended in water. Sodium 10 bicarbonate solution was added until the pH was 10, and the crystals were collected by filtration. Flash chromatography (5/95 methanol/dichloromethane) afforded 91.5 mg (33 %) 4-methoxy-7- $\{(1S,4S)$ -(2-oxa-5-aza-bicyclo[2.2.1]hept-5-yl)}-benzothiazol-2-ylamine as an off-white crystalline solid. ES-MS m/e (%): 278 (M+H<sup>+</sup>, 100).

15    f) N-[4-Methoxy-7- $\{(1S,4S)$ -(2-oxa-5-aza-bicyclo[2.2.1]hept-5-yl)}-benzothiazol-2-yl]-2-methylisonicotinamide

To a stirred solution of 111 mg (0.40 mmol) 4-methoxy-7- $\{(1S,4S)$ -(2-oxa-5-aza-bicyclo[2.2.1]hept-5-yl)}-benzothiazol-2-ylamine and 0.26 ml (1.50 mmol) *N*-ethyldiisopropylamine in 20 ml THF at room temperature was added dropwise a solution of 127 mg (0.66 mmol) 2-methyl-isonicotinoyl hydrochloride in 20 ml 20 dichloromethane and stirring continued at room temperature for 24 h. The reaction mixture was then concentrated *in vacuo*. Flash chromatography (3/97 methanol/ethyl acetate) followed by trituration in ether afforded 142 mg (90 %) *N*-[4-methoxy-7- $\{(1S,4S)$ -(2-oxa-5-aza-bicyclo[2.2.1]hept-5-yl)}-benzothiazol-2-yl]-2-methylisonicotinamide as a yellow crystalline solid. ES-MS m/e (%): 419 (M+Na<sup>+</sup>, 17), 397 (M+H<sup>+</sup>, 100).

25

Example 8

{4-Methoxy-7-[(pyridin-2-ylmethyl)-amino]-benzothiazol-2-yl}-carbamic acid methyl ester

a) (4-Methoxy-benzothiazol-2-yl)-carbamic acid methyl ester

To a stirred solution of 23.6 g (131 mmol) 2-amino-4-methoxybenzothiazole and 12.6 ml (157 mmol) pyridine in 230 ml dichloromethane at 0 °C was added dropwise 10.6 ml (137 mmol) methyl chloroformate and stirring continued for 1 hour. The mixture was then poured onto 1 M hydrochloric acid and the organic phase was separated, washed with brine, dried over sodium sulfate, and concentrated *in vacuo* to afford 31.0 g (99 %) (4-

- 26 -

methoxy-benzothiazol-2-yl)-carbamic acid methyl ester as a white solid. ES-MS m/e (%): 239 (M+H<sup>+</sup>, 100).

b) (4-Methoxy-7-nitro-benzothiazol-2-yl)-carbamic acid methyl ester

To a stirred solution of 13.6 g (57.1 mmol) (4-methoxy-benzothiazol-2-yl)-carbamic acid methyl ester in 300 ml acetic acid at room temperature was added 200 ml 65 % nitric acid and the mixture heated at 70 °C for 4 h. The mixture was then poured onto stirred ice-water and the resulting slurry was filtered. The filter-cake was dissolved in THF and 5 N sodium hydroxide solution was added until the pH was 8. This mixture was then stirred for 1 h, filtered, and the filter-cake dried *in vacuo* to afford 7.61 g (47 %) (4-methoxy-7-nitro-benzothiazol-2-yl)-carbamic acid methyl ester as a yellow crystalline solid. Meanwhile, the filtrate was separated into its aqueous and organic phases and the organic phase was dried over sodium sulfate and concentrated *in vacuo*. The residue was resuspended in 200 ml THF and 200 ml methanol and heated at 70 °C overnight. The mixture was then cooled to room temperature and the resulting crystals were collected by filtration, washed with THF, and dried *in vacuo* to afford a further 1.50 g (9 %) of product as a yellow crystalline solid. ES-MS m/e (%): 306 (M+Na<sup>+</sup>, 28), 284 (M+H<sup>+</sup>, 100).

c) (7-Amino-4-methoxy-benzothiazol-2-yl)-carbamic acid methyl ester

To a stirred solution of 5.00 g (17.7 mmol) (4-methoxy-7-nitro-benzothiazol-2-yl)-carbamic acid methyl ester in 140 ml methanol and 140 ml dichloromethane was added 1.5 g platinum(IV) oxide and the mixture was then stirred for 16 hours at room temperature under an atmosphere of hydrogen. The mixture was then filtered and the filtrate concentrated *in vacuo* to afford 4.03 g (90 %) (7-amino-4-methoxy-benzothiazol-2-yl)-carbamic acid methyl ester as a grey crystalline solid. ES-MS m/e (%): 276 (M+Na<sup>+</sup>, 28), 254 (M+H<sup>+</sup>, 100).

d) {4-Methoxy-7-[(pyridin-2-ylmethyl)-amino]-benzothiazol-2-yl}-carbamic acid methyl ester

To a stirred solution of 40 mg (0.16 mmol) (7-amino-4-methoxy-benzothiazol-2-yl)-carbamic acid methyl ester in 2 ml DMF at room temperature were added 66 mg (0.47 mmol) potassium carbonate and 40 mg (0.16 mmol) 2-(bromomethyl)pyridine hydrobromide and the mixture heated at 70 °C for 16 h. The mixture was then concentrated *in vacuo*. Flash chromatography (2/1 ethyl acetate/hexane) afforded 20 mg (37 %) {4-methoxy-7-[(pyridin-2-ylmethyl)-amino]-benzothiazol-2-yl}-carbamic acid methyl ester as a yellow solid. ES-MS m/e (%): 367 (M+Na<sup>+</sup>, 54), 345 (M+H<sup>+</sup>, 100).

- 27 -

Example 9

*N*-[4-Methoxy-7-(4-methyl-benzylamino)-benzothiazol-2-yl]-benzamide

and

Example 10

5    *N*-{7-[Acetyl-(4-methyl-benzyl)-amino]-4-methoxy-benzothiazol-2-yl}-benzamide

a) 4-Methoxy-3-nitro-phenylamine

To a stirred solution of 30.0 g (244 mmol) *p*-anisidine in 105 ml concentrated sulfuric acid at 0 °C was added 17.6 g (292 mmol) urea. After stirring for 1 h, a solution of 27.1 g (268 mmol) potassium nitrate in 47 ml concentrated sulfuric acid was then added dropwise over 10 1 h while the reaction mixture was maintained at 5-10 °C. The mixture was then poured onto ice, and sodium hydroxide pellets added portionwise with stirring until the pH was 14. Ethyl acetate was then added and the phases were separated. The organic phase was washed with water and then with brine, dried over sodium sulfate, and concentrated *in vacuo* to afford 31.4 g (77 %) 4-methoxy-3-nitro-phenylamine as an orange solid. EI-MS 15 m/e (%): 169 ( $M^+$ , 100), 153 ( $[M-CH_3]^+$ , 10), 92 (21).

b) (4-Methoxy-3-nitro-phenyl)-bis-(4-methyl-benzyl)-amine

To a stirred solution of 5.00 g (29.7 mmol) 4-methoxy-3-nitro-phenylamine in 60 ml acetonitrile at 0 °C were added 10.2 ml (59.5 mmol) *N*-ethyldiisopropylamine and 11.6 g (62.4 mmol) 4-methylbenzyl bromide. Stirring was continued at room temperature for 16 20 h and then the mixture was diluted with ethyl acetate and washed with 0.5 N hydrochloric acid and then with brine. The organic phase was dried over sodium sulfate and concentrated *in vacuo* to afford 10.4 g (93 %) (4-methoxy-3-nitro-phenyl)-bis-(4-methylbenzyl)-amine as an orange oil. ES-MS m/e (%): 399 ( $M+Na^+$ , 18), 377 ( $M+H^+$ , 100).

c) 4-Methoxy-*N*1,*N*1-bis-(4-methyl-benzyl)-benzene-1,3-diamine

25    To a stirred solution of 500 mg (1.33 mmol) (4-methoxy-3-nitro-phenyl)-bis-(4-methylbenzyl)-amine in 20 ml ethanol at room temperature were added 1.91 g (29.2 mmol) zinc powder and 147 mg (1.33 mmol) calcium chloride and the mixture was then heated at 90 °C for 16 hours. The mixture was then filtered and the filtrate diluted with ethyl acetate and washed with 0.5 N sodium hydroxide solution and then with brine. The organic phase 30 was dried over sodium sulfate and concentrated *in vacuo* to afford 420 mg (91 %) 4-methoxy-*N*1,*N*1-bis-(4-methyl-benzyl)-benzene-1,3-diamine as a dark brown oil. ES-MS m/e (%): 347 ( $M+H^+$ , 100).

- 28 -

d) 1-Benzoyl-3-{5-[bis-(4-methyl-benzyl)-amino]-2-methoxy-phenyl}-thiourea

To a stirred solution of 400 mg (1.15 mmol) 4-methoxy-N1,N1-bis-(4-methyl-benzyl)-benzene-1,3-diamine in 8 ml acetone was added dropwise a solution of 0.18 ml (1.34 mmol) benzoyl isothiocyanate in 4 ml acetone and stirring continued for 30 minutes at room temperature. The mixture was then diluted with ethyl acetate and washed with water and then with brine. The organic phase was dried over sodium sulfate and concentrated *in vacuo*. Flash chromatography (1/9 ethyl acetate/hexane) afforded 320 mg (80 %) 1-benzoyl-3-{5-[bis-(4-methyl-benzyl)-amino]-2-methoxy-phenyl}-thiourea as a yellow oil. ES-MS m/e (%): 510 (M+H<sup>+</sup>, 100).

10 e) N-{7-[Bis-(4-methyl-benzyl)-amino]-4-methoxy-benzothiazol-2-yl}-benzamide

To a stirred solution of 500 mg (0.98 mmol) 1-benzoyl-3-{5-[bis-(4-methyl-benzyl)-amino]-2-methoxy-phenyl}-thiourea in 7 ml chloroform was added dropwise 0.050 ml (0.98 mmol) bromine and the reaction mixture heated at reflux for 18 hours. The mixture was then diluted with ethyl acetate and washed with water and then with brine. The organic phase was dried over sodium sulfate and concentrated *in vacuo*. Flash chromatography (ethyl acetate/hexane) afforded 290 mg (58 %) N-{7-[bis-(4-methyl-benzyl)-amino]-4-methoxy-benzothiazol-2-yl}-benzamide as a yellow solid. ES-MS m/e (%): 394 (M+Na<sup>+</sup>, 14), 508 (M+H<sup>+</sup>, 100).

f) (2-Benzoylamino-4-methoxy-benzothiazol-7-yl)-(4-methyl-benzyl)-carbamic acid  
2,2,2-trichloro-ethyl ester

To a stirred solution of 300 mg (0.59 mmol) N-{7-[bis-(4-methyl-benzyl)-amino]-4-methoxy-benzothiazol-2-yl}-benzamide in 10 ml acetonitrile was added dropwise 0.60 ml (4.46 mmol) 2,2,2-trichloroethyl chloroformate and the reaction mixture heated at 80 °C for 72 h. The mixture was then concentrated *in vacuo*. Flash chromatography (ethyl acetate/hexane) afforded 138 mg (40 %) (2-benzoylamino-4-methoxy-benzothiazol-7-yl)-(4-methyl-benzyl)-carbamic acid 2,2,2-trichloro-ethyl ester as a yellow solid. ES-MS m/e (%): 584 (M{<sup>37</sup>Cl, <sup>37</sup>Cl, <sup>37</sup>Cl}+H<sup>+</sup>, 5), 582 (M{<sup>37</sup>Cl, <sup>37</sup>Cl, <sup>35</sup>Cl}+H<sup>+</sup>, 32), 580 (M{<sup>37</sup>Cl, <sup>35</sup>Cl, <sup>35</sup>Cl}+H<sup>+</sup>, 100), 578 (M{<sup>35</sup>Cl, <sup>35</sup>Cl, <sup>35</sup>Cl}+H<sup>+</sup>, 92).

g) N-[4-Methoxy-7-(4-methyl-benzylamino)-benzothiazol-2-yl]-benzamide and N-{7-[Acetyl-(4-methyl-benzyl)-amino]-4-methoxy-benzothiazol-2-yl}-benzamide

To a stirred solution of 100 mg (0.17 mmol) (2-benzoylamino-4-methoxy-benzothiazol-7-yl)-(4-methyl-benzyl)-carbamic acid 2,2,2-trichloro-ethyl ester in 3 ml acetic acid at room temperature was added 90 mg (1.34 mmol) activated zinc powder and the mixture was heated at 80 °C for 16 hours. The mixture was then filtered and the filtrate concentrated *in*

- 29 -

*vacuo*. Flash chromatography (ethyl acetate/hexane) afforded 15 mg (21 %) *N*-[4-methoxy-7-(4-methyl-benzylamino)-benzothiazol-2-yl]-benzamide as a yellow crystalline solid, ES-MS m/e (%): 426 ( $M+Na^+$ , 27), 404 ( $M+H^+$ , 100), and 10 mg (13 %) *N*-{7-[acetyl-(4-methyl-benzyl)-amino]-4-methoxy-benzothiazol-2-yl}-benzamide as a yellow crystalline solid, ES-MS m/e (%): 468 ( $M+Na^+$ , 12), 446 ( $M+H^+$ , 100).

#### Example 11

##### 4-{{[(2-Methoxy-ethyl)-methyl-amino]-methyl}-N-{4-methoxy-7-[(2-methoxy-ethyl)-methyl-amino]-benzothiazol-2-yl}-benzamide dihydrochloride

A mixture of 100 mg (0.24 mmol) 4-chloromethyl-*N*-{4-methoxy-7-[(2-methoxy-ethyl)-methyl-amino]-benzothiazol-2-yl}-benzamide and 212 mg (2.38 mmol) *N*-(2-methoxyethyl)methylamine was ultrasonicated at room temperature for 30 minutes. The reaction mixture was then concentrated *in vacuo* and the residue purified by flash chromatography (ethyl acetate). The product-containing fractions were concentrated *in vacuo* and the residue stirred with HCl in ether and ethyl acetate. The resulting crystals were collected by filtration and washed with ether to afford 110 mg (91 %) 4-{{[(2-methoxy-ethyl)-methyl-amino]-methyl}-N-{4-methoxy-7-[(2-methoxy-ethyl)-methyl-amino]-benzothiazol-2-yl}-benzamide dihydrochloride as a white crystalline solid. ES-MS m/e (%): 473 ( $M+H^+$ , 100).

#### Example 12

20) *N*-(7-Dimethylamino-4-methoxy-benzothiazol-2-yl)-4-fluoro-benzamide

##### a) 4-Methoxy-benzothiazole-2,7-diamine

To a suspension of 4.28 g (16.9 mmol) (7-amino-4-methoxy-benzothiazol-2-yl)-carbamic acid methyl ester in 100 ml dioxane and 50 ml ethylene glycol was added 100 ml 5 N NaOH and the mixture was heated at 100 °C for 16 h. After cooling to room temperature, 25) the reaction mixture was concentrated *in vacuo* and the residue diluted with 300 ml tetrahydrofuran and stirred for 10 minutes. The mixture was filtered and the filtrate concentrated *in vacuo*. The residue was triturated in ether to afford 2.73 g (83%) 4-methoxy-benzothiazole-2,7-diamine as a brown solid. ES-MS m/e (%): 196 ( $M+H^+$ , 100).

##### b) 4-Methoxy-*N*7,*N*7-dimethyl-benzothiazole-2,7-diamine

30) To a stirred solution of 2.00 g (1.02 mmol) 4-methoxy-benzothiazole-2,7-diamine in 30 ml DMF at room temperature was added 4.25 g (3.07 mmol) potassium carbonate and the mixture heated to 50 °C. A solution of 0.64 ml (1.02 mmol) iodomethane in 10 ml DMF was then added dropwise over 3 h and stirring continued for a further 1 h at 50 °C. The

- 30 -

mixture was then filtered and the filtrate concentrated *in vacuo*. Flash chromatography (20/1 dichloromethane/methanol) afforded 600 mg (26 %) 4-methoxy-*N*7,*N*7-dimethylbenzothiazole-2,7-diamine as a yellow solid, ES-MS m/e (%): 224 ( $M+H^+$ , 100); 540 mg (25 %) 4-methoxy-*N*7-methyl-benzothiazole-2,7-diamine as a yellow solid, ES-MS m/e (%) 5: 210 ( $M+H^+$ , 100) and 340 mg (17 %) recovered starting material

c) *N*-(7-Dimethylamino-4-methoxy-benzothiazol-2-yl)-4-fluoro-benzamide

To a stirred solution of 41 mg (0.29 mmol) 4-fluoro-benzoic acid in 1 ml THF were added 128 mg (0.34 mmol) HATU and 0.10 ml (0.56 mmol) *N*-ethyldiisopropylamine and stirring continued at room temperature for 2.5 h. 50 mg (0.22 mmol) 4-methoxy-*N*7,*N*7-dimethyl-benzothiazole-2,7-diamine was then added and stirring continued at room 10 temperature for 16 h. The reaction mixture was then concentrated *in vacuo*. Flash chromatography (ethyl acetate/hexane) afforded 64 mg (83 %) *N*-(7-dimethylamino-4-methoxy-benzothiazol-2-yl)-4-fluoro-benzamide as a white crystalline solid. ES-MS m/e (%) 10: 346 ( $M+H^+$ , 100).

15 In an analogous manner there were obtained:

Example 13

*N*-(7-Diethylamino-4-methoxy-benzothiazol-2-yl)-4-fluoro-benzamide

From 4-methoxy-benzothiazole-2,7-diamine with potassium carbonate and iodoethane in DMF, then treatment with 4-fluoro-benzoic acid, HATU and *N*-ethyldiisopropylamine in 20 THF. ES-MS m/e (%): 374 ( $M+H^+$ , 100).

Example 14

*N*-[7-(Benzyl-methyl-amino)-4-methoxy-benzothiazol-2-yl]-4-fluoro-benzamide

From 4-methoxy-*N*7-methyl-benzothiazole-2,7-diamine with potassium carbonate and benzyl bromide in DMF, then treatment with 4-fluoro-benzoic acid, HATU and *N*-ethyldiisopropylamine in THF. ES-MS m/e (%): 422 ( $M+H^+$ , 100). 25

Example 15

4-Fluoro-*N*-[4-methoxy-7-(methyl-pyridin-2-ylmethyl-amino)-benzothiazol-2-yl]-benzamide

From 4-methoxy-*N*7-methyl-benzothiazole-2,7-diamine with potassium carbonate and 2-30 (bromomethyl)pyridine hydrobromide in DMF, then treatment with 4-fluoro-benzoic acid, HATU and *N*-ethyldiisopropylamine in THF. ES-MS m/e (%): 423 ( $M+H^+$ , 100).

- 31 -

Example 16

*N*-(7-(Benzyl-methyl-amino)-4-methoxy-benzothiazol-2-yl]-2-methyl-isonicotinamide

From 4-methoxy-*N*7-methyl-benzothiazole-2,7-diamine with potassium carbonate and benzyl bromide in DMF, then treatment with 2-methyl-isonicotinic acid hydrochloride, 5 HATU and *N*-ethyldiisopropylamine in THF. ES-MS m/e (%): 419 ( $M+H^+$ , 100).

Example 17

*N*-(7-(Dimethylcarbamoylmethyl-methyl-amino)-4-methoxy-benzothiazol-2-yl]-4-fluoro-benzamide

From 4-methoxy-*N*7-methyl-benzothiazole-2,7-diamine with potassium carbonate and 2-10 iodo-*N,N*-dimethyl-acetamide in DMF, then treatment with 4-fluorobenzoic acid, HATU and *N*-ethyldiisopropylamine in THF. ES-MS m/e (%): 417 ( $M+H^+$ , 100).

Example 18

*N*-(7-Diethylamino-4-methoxy-benzothiazol-2-yl)-2-methyl-isonicotinamide

From 4-methoxy-benzothiazole-2,7-diamine with potassium carbonate and iodoethane in 15 DMF, then treatment with 2-methyl-isonicotinic acid hydrochloride, HATU and *N*-ethyldiisopropylamine in THF. ES-MS m/e (%): 371 ( $M+H^+$ , 100).

Example 19

*N*-(7-(Acetyl-methyl-amino)-4-methoxy-benzothiazol-2-yl]-4-fluoro-benzamide

a) *N*-(2-Amino-4-methoxy-benzothiazol-7-yl)-*N*-methyl-acetamide

20 To a stirred solution of 120 mg (0.57 mmol) 4-methoxy-*N*7-methyl-benzothiazole-2,7-diamine in 1 ml dichloromethane and 1 ml tetrahydrofuran at 0 °C was added 0.09 ml (1.15 mmol) pyridine. A solution of 0.04 ml (0.57 mmol) acetyl chloride in 1 ml dichloromethane was then added dropwise and stirring continued for 3 h at 0 °C. The mixture was then concentrated *in vacuo*. Flash chromatography (30/1 dichloromethane/methanol) afforded 60 mg (42 %) *N*-(2-amino-4-methoxy-benzothiazol-7-yl)-*N*-methyl-acetamide as a light brown crystalline solid, ES-MS m/e (%): 252 ( $M+H^+$ , 100).

b) *N*-(7-(Acetyl-methyl-amino)-4-methoxy-benzothiazol-2-yl]-4-fluoro-benzamide

- 32 -

To a stirred solution of 31 mg (0.22 mmol) 4-fluoro-benzoic acid in 2 ml THF were added 89 mg (0.23 mmol) HATU and 0.07 ml (0.44 mmol) *N*-ethyldiisopropylamine and stirring continued at room temperature for 2 h. 28 mg (0.11 mmol) *N*-(2-amino-4-methoxy-benzothiazol-7-yl)-*N*-methyl-acetamide was then added and stirring continued 5 at 50 °C for 16 h. The reaction mixture was then concentrated *in vacuo*. Flash chromatography (dichloromethane/methanol 50/1) followed by trituration in ether afforded 10 mg (24 %) *N*-[7-(acetyl-methyl-amino)-4-methoxy-benzothiazol-2-yl]-4-fluoro-benzamide as a white crystalline solid. ES-MS m/e (%): 374 (M+H<sup>+</sup>, 100).

Analogously to Example 12 there was obtained:

10

#### Example 20

*N*-[7-(Dimethylcarbamoylmethyl-ethyl-amino)-4-methoxy-benzothiazol-2-yl]-4-fluoro-benzamide

From *N*7-ethyl-4-methoxy-benzothiazole-2,7-diamine with potassium carbonate and 2-iodo-*N,N*-dimethyl-acetamide in DMF, then treatment with 4-fluorobenzoic acid, HATU 15 and *N*-ethyldiisopropylamine in THF. ES-MS m/e (%): 431 (M+H<sup>+</sup>, 100).

Analogously to Example 19 there were obtained:

#### Example 21

*N*-[7-(Acetyl-ethyl-amino)-4-methoxy-benzothiazol-2-yl]-4-fluoro-benzamide

From *N*7-ethyl-4-methoxy-benzothiazole-2,7-diamine with pyridine and acetyl chloride in dichloromethane and THF, then treatment with 4-fluorobenzoic acid, HATU and *N*-methylmorpholine in THF. ES-MS m/e (%): 388 (M+H<sup>+</sup>, 100).

#### Example 22

*N*-[7-(Acetyl-ethyl-amino)-4-methoxy-benzothiazol-2-yl]-2-methyl-isonicotinamide

From *N*7-ethyl-4-methoxy-benzothiazole-2,7-diamine with pyridine and acetyl chloride in dichloromethane and THF, then treatment with 2-methyl-isonicotinic acid hydrochloride, HATU and *N*-methylmorpholine in THF. ES-MS m/e (%): 385 (M+H<sup>+</sup>, 100).

Analogously to Example 12 there was obtained:

#### Example 23

*N*-[7-(Benzyl-ethyl-amino)-4-methoxy-benzothiazol-2-yl]-4-fluoro-benzamide

- 33 -

From *N*7-ethyl-4-methoxy-benzothiazole-2,7-diamine with potassium carbonate and benzyl bromide in DMF, then treatment with 4-fluorobenzoic acid, HATU and *N*-ethyldiisopropylamine in THF. ES-MS m/e (%): 436 ( $M+H^+$ , 100).

Analogously to Example 19 there were obtained:

5

#### Example 24

*N*-[7-(Acetyl-benzyl-amino)-4-methoxy-benzothiazol-2-yl]-4-fluoro-benzamide

From *N*7-benzyl-4-methoxy-benzothiazole-2,7-diamine with pyridine and acetyl chloride in dichloromethane and THF, then treatment with 4-fluorobenzoic acid, HATU and *N*-methylmorpholine in THF. ES-MS m/e (%): 450 ( $M+H^+$ , 100).

10

#### Example 25

*N*-[7-(Acetyl-benzyl-amino)-4-methoxy-benzothiazol-2-yl]-2-bromo-isonicotinamide

From *N*7-benzyl-4-methoxy-benzothiazole-2,7-diamine with pyridine and acetyl chloride in dichloromethane and THF, then treatment with 2-bromo-isonicotinic acid, HATU and *N*-methylmorpholine in THF. ES-MS m/e (%): 513 ( $M\{^{81}Br\}+H^+$ , 90), 511 ( $M\{^{79}Br\}+H^+$ , 100).

15

#### Example 26

*N*-{7-[Acetyl-(2-methoxy-ethyl)-amino]-4-methoxy-benzothiazol-2-yl}-4-fluoro-benzamide

From 4-methoxy-*N*7-(2-methoxy-ethyl)-benzothiazole-2,7-diamine with pyridine and acetyl chloride in dichloromethane and THF, then treatment with 4-fluoro-benzoic acid, HATU and *N*-methylmorpholine in THF. ES-MS m/e (%): 418 ( $M+H^+$ , 90), 100).

20

#### Example 27

*N*-{7-[Acetyl-(2-methoxy-ethyl)-amino]-4-methoxy-benzothiazol-2-yl}-2-bromo-isonicotinamide

25

From 4-methoxy-*N*7-(2-methoxy-ethyl)-benzothiazole-2,7-diamine with pyridine and acetyl chloride in dichloromethane and THF, then treatment with 2-bromo-isonicotinic acid, HATU and *N*-methylmorpholine in THF. ES-MS m/e (%): 481 ( $M\{^{81}Br\}+H^+$ , 100), 479 ( $M\{^{79}Br\}+H^+$ , 99).

- 34 -

Example 28

4-Fluoro-N-{4-methoxy-7-[(4-methoxy-benzyl)-methyl-amino]-benzothiazol-2-yl}-benzamide

From 4-methoxy-N7-methyl-benzothiazole-2,7-diamine with potassium carbonate and 4-methoxybenzyl chloride in DMF, then treatment with 4-fluorobenzoic acid, HATU and *N*-ethyldiisopropylamine in THF. ES-MS m/e (%): 452 ( $M+H^+$ , 100).

Example 29

2-Bromo-N-{4-methoxy-7-[(4-methoxy-benzyl)-methyl-amino]-benzothiazol-2-yl}-isonicotinamide

From 4-methoxy-N7-methyl-benzothiazole-2,7-diamine with potassium carbonate and 4-methoxybenzyl chloride in DMF, then treatment with 2-bromo-isonicotinic acid, HATU and *N*-ethyldiisopropylamine in THF. ES-MS m/e (%): 515 ( $M\{^{81}Br\}+H^+$ , 100), 513 ( $M\{^{79}Br\}+H^+$ , 81).

Example 30

15 *N*-{4-Methoxy-7-[(4-methoxy-benzyl)-methyl-amino]-benzothiazol-2-yl}-2-methylisonicotinamide

From 4-methoxy-N7-methyl-benzothiazole-2,7-diamine with potassium carbonate and 4-methoxybenzyl chloride in DMF, then treatment with 2-methyl-isonicotinic acid hydrochloride, HATU and *N*-ethyldiisopropylamine in THF. ES-MS m/e (%): 449 ( $M+H^+$ , 100).

Example 31

4-Fluoro-N-{4-methoxy-7-[methyl-(2-oxo-2-piperidin-1-yl-ethyl)-amino]-benzothiazol-2-yl}-benzamide

From 4-methoxy-benzothiazole-2,7-diamine with potassium carbonate and 2-iodo-1-morpholin-4-yl-ethanone in DMF, then treatment with potassium carbonate and iodomethane in DMF, then treatment with 4-fluorobenzoic acid, HATU and *N*-ethyldiisopropylamine in THF. ES-MS m/e (%): 457 ( $M+H^+$ , 100).

Example 32

*N*-[7-(Benzyl-methyl-amino)-4-methoxy-benzothiazol-2-yl]-2-bromo-isonicotinamide

- 35 -

From 4-methoxy-N7-methyl-benzothiazole-2,7-diamine with potassium carbonate and benzyl bromide in DMF, then treatment with 2-bromo-isonicotinic acid, HATU and *N*-ethyldiisopropylamine in THF. ES-MS m/e (%): 485 ( $M\{^{81}Br\}+H^+$ , 98), 483 ( $M\{^{79}Br\}+H^+$ , 100).

5

### Example 33

2-Bromo-N-{4-methoxy-7-[methyl-(tetrahydro-pyran-4-ylmethyl)-amino]-benzothiazol-2-yl}-isonicotinamide

a) (4-Methoxy-3-nitro-phenyl)-methyl-(tetrahydro-pyran-4-ylmethyl)-amine

To a stirred solution of 4.70 g (20.0 mmol) 4-bromo-2-nitro-anisole in 100 ml dioxane were added 4.03 g (24.3 mmol) methyl-(tetrahydro-pyran-4-ylmethyl)-amine hydrochloride (1:1), 0.710 g (20.0 mmol) 2-(dicyclohexylphosphino)biphenyl, 16.5 g (50.65 mmol) cesium carbonate, and 227 mg (1.0 mmol) palladium(II) acetate. The mixture was heated at reflux for 24 h and then poured onto water and extracted three times with ethyl acetate. The combined organic phases were dried over sodium sulfate and concentrated *in vacuo*. Flash chromatography (1/1 hexane/ethyl acetate) afforded 3.5 g (62 %) (4-methoxy-3-nitro-phenyl)-methyl-(tetrahydro-pyran-4-ylmethyl)-amine as a red oil. ES-MS m/e (%): 281 ( $M+H^+$ , 100).

b) 4-Methoxy-N1-methyl-N1-(tetrahydro-pyran-4-ylmethyl)-benzene-1,3-diamine

To a stirred solution of 3.5 g (12.5 mmol) (4-methoxy-3-nitro-phenyl)-methyl-(tetrahydro-pyran-4-ylmethyl)-amine in 230 ml methanol was added 70 mg 10 % palladium on charcoal and the mixture was then stirred for 18 hours at room temperature under an atmosphere of hydrogen. The mixture was then filtered and the filtrate concentrated *in vacuo* to afford 2.20 g (70 %) 4-methoxy-N1-methyl-N1-(tetrahydro-pyran-4-ylmethyl)-benzene-1,3-diamine as a dark brown oil. ES-MS m/e (%): 251 ( $M+H^+$ , 100).

c) 1-Benzoyl-3-{2-methoxy-5-[methyl-(tetrahydro-pyran-4-ylmethyl)-amino]-phenyl}-thiourea

To a stirred solution of 1.70 g (6.8 mmol) 4-methoxy-N1-methyl-N1-(tetrahydro-pyran-4-ylmethyl)-benzene-1,3-diamine in 30 ml acetone was added dropwise 1.0 ml (7.50 mmol) benzoyl isothiocyanate and stirring continued for 1 h at room temperature. The mixture was then concentrated *in vacuo* and the residue subjected to column chromatography (1/1 hexane/ethyl acetate) to afford 2.0 g (71 %) 1-benzoyl-3-{2-methoxy-5-[methyl-

- 36 -

(tetrahydro-pyran-4-ylmethyl)-amino]-phenyl}-thiourea as a yellow oil. ES-MS m/e (%): 436 (M+Na<sup>+</sup>, 13), 414 (M+H<sup>+</sup>, 100).

d) {2-Methoxy-5-[methyl-(tetrahydro-pyran-4-ylmethyl)-amino]-phenyl}-thiourea

To a stirred suspension of 2.0 g (4.8 mmol) 1-benzoyl-3-{2-methoxy-5-[methyl-(tetrahydro-pyran-4-ylmethyl)-amino]-phenyl}-thiourea in 15 ml methanol was added dropwise 0.4 ml (7.25 mmol) 5.4 M sodium methylate solution and stirring continued for 18 hrs at room temperature. The mixture was then concentrated *in vacuo* and the residue subjected to column chromatography (1/1 hexane/ethyl acetate) to afford 1.5 g (100 %) {2-methoxy-5-[methyl-(tetrahydro-pyran-4-ylmethyl)-amino]-phenyl}-thiourea as a beige oil. ES-MS m/e (%): 310 (M+H<sup>+</sup>, 100).

e) 4-Methoxy-N7-methyl-N7-(tetrahydro-pyran-4-ylmethyl)-benzothiazole-2,7-diamine

1.5 g (0.53 mmol) {2-methoxy-5-[methyl-(tetrahydro-pyran-4-ylmethyl)-amino]-phenyl}-thiourea were dissolved in 15 ml chloroform and at room temperature 0.025 ml (0.5 mmol) Br<sub>2</sub> were added slowly. After 24 hrs of reflux the mixture was concentrated *in vacuo* and the residue suspended in water. Sodium bicarbonate solution was added until the pH was 10, and the crystals were collected by filtration. These were subjected to column chromatography (1/1 hexane/ethyl acetate) to afford 0.16 g (10 %) of 4-methoxy-N7-methyl-N7-(tetrahydro-pyran-4-ylmethyl)-benzothiazole-2,7-diamine as brown solid. ES-MS m/e (%): 308 (M+H<sup>+</sup>, 100).

f) 2-Bromo-N-{4-methoxy-7-[methyl-(tetrahydro-pyran-4-ylmethyl)-amino]-benzothiazol-2-yl}-isonicotinamide

To a stirred solution of 99 mg (0.49 mmol) 2-bromo-isonicotinic acid in 3 ml THF were added 195 mg (0.51 mmol) HATU and 0.11ml (0.98 mmol) N-methylmorpholine and stirring continued at 30 °C for 5 h. 75 mg (0.24 mmol) 4-methoxy-N7-methyl-N7-(tetrahydro-pyran-4-ylmethyl)-benzothiazole-2,7-diamine was then added and stirring continued at 40 °C for 16 h. The reaction mixture was then diluted with ethyl acetate and washed sequentially with 0.5 N hydrochloric acid, saturated sodium bicarbonate solution and brine. The organic phase was dried over sodium sulfate and concentrated *in vacuo*. Flash chromatography (methanol/dichloromethane) followed by trituration in ether/hexane afforded 17 mg (14%) 2-bromo-N-{4-methoxy-7-[methyl-(tetrahydro-pyran-4-ylmethyl)-amino]-benzothiazol-2-yl}-isonicotinamide as a white crystalline solid. ES-MS m/e (%): 493 (M{<sup>81</sup>Br}+ H<sup>+</sup>, 100), 491 (M{<sup>79</sup>Br}+H<sup>+</sup>, 95).

In an analogous manner there was obtained:

- 37 -

### Example 34

4-Fluoro-N-{4-methoxy-7-[methyl-(tetrahydro-pyran-4-ylmethyl)-amino]-benzothiazol-2-yl}-benzamide

From 4-methoxy-N7-methyl-N7-(tetrahydro-pyran-4-ylmethyl)-benzothiazole-2,7-diamine with 4-fluorobenzoic acid, HATU and *N*-ethyldiisopropylamine in THF. ES-MS m/e (%): 430 ( $M+H^+$ , 100).

Analogously to Example 6 there were obtained:

### Example 35

*N*-[7-(Benzyl-methyl-amino)-4-methoxy-benzothiazol-2-yl]-2-morpholin-4-yl-isonicotinamide

From *N*-[7-(benzyl-methyl-amino)-4-methoxy-benzothiazol-2-yl]-2-bromo-isonicotinamide with morpholine and cesium carbonate. ES-MS m/e (%): 490 ( $M+H^+$ , 100).

### Example 36

15 2-Bromo-*N*{4-methoxy-7-[methyl-(tetrahydro-pyran-4-yl)-amino]-benzothiazol-2-yl}-isonicotinamide

a) (4-Methoxy-3-nitro-phenyl)-methyl-(tetrahydro-pyran-4-yl)-amine

To a stirred solution of 7.50 g (32.0 mmol) 4-bromo-2-nitro-anisole in 200 ml dioxane were added 6.86 g (45.0 mmol) methyl-(tetrahydro-pyran-4-yl)-amine hydrochloride (1:1), 1.13 g (3.0 mmol) 2-(dicyclohexylphosphino)biphenyl, 14.75 g (45.0 mmol) cesium carbonate, and 360 mg (2.0 mmol) palladium(II) acetate. The mixture was heated at reflux for 72 h and then poured onto water and extracted three times with ethyl acetate. The combined organic phases were dried over sodium sulfate and concentrated *in vacuo*. Flash chromatography (1/2 hexane/ethyl acetate) afforded 1.59 g (18.5 %) (4-methoxy-3-nitro-phenyl)-methyl-(tetrahydro-pyran-4-yl)-amine as a red solid. ES-MS m/e (%): 267 ( $M+H^+$ , 100).

b) 4-Methoxy-N1-methyl-N1-(tetrahydro-pyran-4-yl)-benzene-1,3-diamine

To a stirred solution of 0.73 g (2.74 mmol) (4-methoxy-3-nitro-phenyl)-methyl-(tetrahydro-pyran-4-yl)-amine in 50 ml methanol was added 15 mg 10 % palladium on charcoal and the mixture was then stirred for 18 hours at room temperature under an atmosphere of hydrogen. The mixture was then filtered and the filtrate concentrated *in*

- 38 -

*vacuo* to afford 0.3520 g (54 %) 4-methoxy-N1-methyl-N1-(tetrahydro-pyran-4-ylmethyl)-benzene-1,3-diamine as an off-white solid. Mp.: 97-99° C.

c) 1-Benzoyl-3-{2-methoxy-5-[methyl-(tetrahydro-pyran-4-yl)-amino]-phenyl}-thiourea

To a stirred solution of 0.330 g (1.4 mmol) 4-methoxy-N1-methyl-N1-(tetrahydro-pyran-4-ylmethyl)-benzene-1,3-diamine in 5 ml acetone was added dropwise 0.2 ml (1.50 mmol) benzoyl isothiocyanate and stirring continued for 16 hrs at room temperature. The mixture was then concentrated *in vacuo* and the residue subjected to column chromatography (1/1 hexane/ethyl acetate) to afford 0.31 g (56 %) 1-benzoyl-3-{2-methoxy-5-[methyl-(tetrahydro-pyran-4-yl)-amino]-phenyl}-thiourea as a yellow solid. ES-MS m/e (%): 422 (M+Na<sup>+</sup>, 13), 400 (M+H<sup>+</sup>, 100).

d) {2-Methoxy-5-[methyl-(tetrahydro-pyran-4-yl)-amino]-phenyl}-thiourea

To a stirred suspension of 1.7 g (4.2 mmol) 1-benzoyl-3-{2-methoxy-5-[methyl-(tetrahydro-pyran-4-yl)-amino]-phenyl}-thiourea in 13 ml methanol was added dropwise 0.78 ml (6.35 mmol) 5.4 M sodium methylate solution and stirring continued for 18 hrs at room temperature. The mixture was then concentrated *in vacuo* and the residue subjected to column chromatography (1/1 hexane/ethyl acetate) to afford 0.6 g (51 %) {2-methoxy-5-[methyl-(tetrahydro-pyran-4-yl)-amino]-phenyl}-thiourea as a yellow solid. ES-MS m/e (%): 296 (M+H<sup>+</sup>, 100).

e) 4-Methoxy-N7-methyl-N7-(tetrahydro-pyran-4-yl)-benzothiazole-2,7-diamine

20 0.28 g (0.95 mmol) {2-methoxy-5-[methyl-(tetrahydro-pyran-4-yl)-amino]-phenyl}-thiourea were dissolved in 15 ml chloroform and 0.05 ml (1.0 mmol) Br<sub>2</sub> were added slowly at room temperature. After 24 hrs of reflux the mixture was concentrated *in vacuo* and the residue suspended in water. Sodium bicarbonate solution was added until the pH was 10, and the crystals were collected by filtration. These were subjected to column chromatography (ethyl acetate) to afford 0.11 g (41 %) of 4-methoxy-N7-methyl-N7-(tetrahydro-pyran-4-yl)-benzothiazole-2,7-diamine as an off-white solid. ES-MS m/e (%): 294 (M+H<sup>+</sup>, 100).

f) 2-Bromo-N-{4-methoxy-7-[methyl-(tetrahydro-pyran-4-yl)-amino]-benzothiazol-2-yl}-isonicotinamide

30 To a stirred solution of 103 mg (0.51 mmol) 2-bromo-isonicotinic acid in 3 ml THF were added 204 mg (0.53 mmol) HATU and 0.11ml (1.02 mmol) N-methylmorpholine and stirring continued at 30 °C for 7 h. 75 mg (0.26 mmol) 4-methoxy-N7-methyl-N7-(tetrahydro-pyran-4-yl)-benzothiazole-2,7-diamine was then added and stirring continued

- 39 -

at 40 °C for 16 h. The reaction mixture was then diluted with ethyl acetate and washed sequentially with saturated sodium bicarbonate solution and brine. The organic phase was dried over sodium sulfate and concentrated *in vacuo*. Flash chromatography (methanol/dichloromethane) followed by trituration in ether/pentane afforded 77 mg  
5 (63%) 2-bromo-N-{4-methoxy-7-[methyl-(tetrahydro-pyran-4-yl)-amino]-benzothiazol-2-yl}-isonicotinamide as a white crystalline solid. ES-MS m/e (%): 479 ( $M\{^{81}\text{Br}\} + \text{H}^+$ , 100), 477 ( $M\{^{79}\text{Br}\} + \text{H}^+$ , 95).

In an analogous manner there was obtained:

Example 37

10 4-Fluoro-N-{4-methoxy-7-[methyl-(tetrahydro-pyran-4-yl)-amino]-benzothiazol-2-yl}-benzamide

From 4-methoxy-N7-methyl-N7-(tetrahydro-pyran-4-ylmethyl)-benzothiazole-2,7-diamine with 4-fluorobenzoic acid, HATU and N-ethyldiisopropylamine in THF. ES-MS m/e (%): 416 ( $M + \text{H}^+$ , 100).

15 Analogously to Example 6 there were obtained:

Example 38

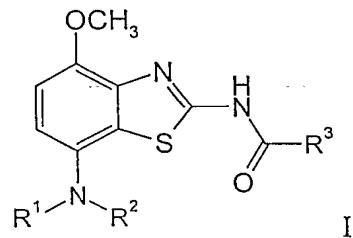
N-{4-Methoxy-7-[methyl-(tetrahydro-pyran-4-yl)-amino]-benzothiazol-2-yl}-2-morpholin-4-yl-isonicotinamide

From 2-bromo-N-{4-methoxy-7-[methyl-(tetrahydro-pyran-4-yl)-amino]-benzothiazol-2-yl}-isonicotinamide with morpholine and cesium carbonate. ES-MS m/e (%): 484 ( $M + \text{H}^+$ , 100).

- 40 -

### Claims

#### 1. Compounds of the general formula



5 wherein

- $R^1, R^2$  are independently from each other hydrogen, lower alkyl,  $C_{3-6}$ -cycloalkyl, tetrahydropyran-2,3 or 4-yl, piperidin-4-yl, optionally substituted by lower alkyl,  $-(CH_2)_n$ -O-lower alkyl,  $-(CH_2)_n$ -NR'R'', -C(O)-lower alkyl,  $-(CH_2)_n$ -C(O)-lower alkyl,  $-(CH_2)_n$ -C(O)- $C_{3-6}$ -cycloalkyl,  $-(CH_2)_n$ -C(O)-NR'R'', 10  $-(CH_2)_n$ -phenyl, optionally substituted by lower alkyl, lower alkoxy or NR'R'' or is  $-(CH_2)_n$ -pyridinyl, optionally substituted by lower alkyl, lower alkoxy or NR'R'', or is  $-(CH_2)_n$ -morpholinyl,  $-(CH_2)_n$ -tetrahydropyran-2,3 or 4-yl,  $-(CH_2)_n$ -piperidin-1 or 4-yl, optionally substituted by lower alkyl, or is 15  $-C(O)-C_{5,6}$ -cycloalkyl, -C(O)-tetrahydropyran-2,3 or 4-yl, -C(O)-morpholinyl,  $-C(O)$ -piperidin-1-yl or  $-C(O)$ -pyrrolidin-1-yl, or  $R^1$  and  $R^2$  form together with the N atom to which they are attached the ring 2-oxa-5-aza-bicyclo[2.2.1]hept-5-yl or an azetidinyl ring, optionally substituted by lower alkyl or lower alkoxy;
- $R^3$  is lower alkoxy, phenyl, optionally substituted by halogen,  $-(CH_2)_n$ -halogen, or by 20  $-(CH_2)_n$ -N(R')-( $CH_2$ )<sub>n+1</sub>-O-lower alkyl, or is pyridinyl, optionally substituted by lower alkyl, halogen or by morpholinyl or is morpholinyl, piperidin-1-yl, disubstituted in the 4 position by lower alkyl and  $-(CH_2)_n$ -OH, or is 2-aza-bicyclo[2.2.2]octane;
- $n$  is 1 or 2;
- 25  $R'/R''$  are independently from each other hydrogen or lower alkyl or together may form with the N atom an azetidinyl-, pyrrolidinyl- or piperidinyl group; and pharmaceutically acceptable acid addition salts thereof.

- 41 -

2. Compounds of formula I in accordance with claim 1, wherein one of R<sup>1</sup>/R<sup>2</sup> is lower alkyl and the other is -(CH<sub>2</sub>)<sub>n</sub>-O-lower alkyl and R<sup>3</sup> is phenyl, optionally substituted by halogen or -(CH<sub>2</sub>)<sub>n</sub>-halogen.

5        3. Compounds of formula I in accordance with claim 2, wherein the compound is  
N-{4-methoxy-7-[(2-methoxy-ethyl)-methyl-amino]-benzothiazol-2-yl}-benzamide,  
4-fluoro-N-{4-methoxy-7-[(2-methoxy-ethyl)-methyl-amino]-benzothiazol-2-yl}-  
benzamide or  
4-chloromethyl-N-{4-methoxy-7-[(2-methoxy-ethyl)-methyl-amino]-benzothiazol-2-yl}-  
10 benzamide.

4. Compounds in accordance with claim 1, wherein wherein one of R<sup>1</sup>/R<sup>2</sup> is lower alkyl and the other is -(CH<sub>2</sub>)<sub>n</sub>-O-lower alkyl or R<sup>1</sup> and R<sup>2</sup> are together with the N atom the group 2-oxa-5-aza-bicyclo[2.2.1]hept-5-yl and R<sup>3</sup> is pyridinyl, substituted by morpholine.

5. Compounds in accordance with claim 4, wherein the compound is  
15 N-{4-methoxy-7-[(2-methoxy-ethyl)-methyl-amino]-benzothiazol-2-yl}-2-morpholin-4-yl-isonicotinamide or  
N-[4-methoxy-7-((1S,4S)-(2-oxa-5-aza-bicyclo[2.2.1]hept-5-yl)}-benzothiazol-2-yl]-2-methyl-isonicotinamide.

6. Compounds in accordance with claim 1, wherein one of R<sup>1</sup>/R<sup>2</sup> is  
20 -C(O)-lower alkyl and the other is lower alkyl, -(CH<sub>2</sub>)<sub>n</sub>-O-lower alkyl or benzyl, optionally substituted by lower alkyl and R<sup>3</sup> is phenyl or pyridinyl, which rings are optionally substituted by halogen or lower alkyl.

7. Compounds in accordance with claim 6, wherein the compound is  
25 N-{7-[acetyl-(4-methyl-benzyl)-amino]-4-methoxy-benzothiazol-2-yl}-benzamide,  
N-[7-(acetyl-methyl-amino)-4-methoxy-benzothiazol-2-yl]-4-fluoro-benzamide,  
N-[7-(acetyl-ethyl-amino)-4-methoxy-benzothiazol-2-yl]-4-fluoro-benzamide,  
N-[7-(acetyl-benzyl-amino)-4-methoxy-benzothiazol-2-yl]-4-fluoro-benzamide,  
N-[7-(acetyl-benzyl-amino)-4-methoxy-benzothiazol-2-yl]-2-bromo-isonicotinamide or  
30 N-{7-[acetyl-(2-methoxy-ethyl)-amino]-4-methoxy-benzothiazol-2-yl}-4-fluoro-benzamide.

8. Compounds in accordance with claim 1, wherein one of R<sup>1</sup>/R<sup>2</sup> is lower alkyl and the other is lower alkyl or benzyl, optionally substituted by lower alkoxy and R<sup>3</sup> is phenyl or pyridinyl, which rings are optionally substituted by morpholinyl, halogen or lower alkyl.

- 42 -

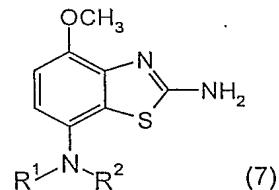
9. Compounds in accordance with claim 8, wherein the compound is  
*N*-(7-dimethylamino-4-methoxy-benzothiazol-2-yl)-4-fluoro-benzamide,  
*N*-[7-(benzyl-methyl-amino)-4-methoxy-benzothiazol-2-yl]-4-fluoro-benzamide,  
*N*-[7-(benzyl-methyl-amino)-4-methoxy-benzothiazol-2-yl]-2-methyl-isonicotinamide,  
5 4-fluoro-*N*-[4-methoxy-7-[(4-methoxy-benzyl)-methyl-amino]-benzothiazol-2-yl]-  
benzamide,  
*N*-{4-methoxy-7-[(4-methoxy-benzyl)-methyl-amino]-benzothiazol-2-yl}-2-methyl-  
isonicotinamide,  
*N*-[7-(benzyl-methyl-amino)-4-methoxy-benzothiazol-2-yl]-2-bromo-isonicotinamide or  
10 *N*-[7-(benzyl-methyl-amino)-4-methoxy-benzothiazol-2-yl]-2-morpholin-4-yl-  
isonicotinamide.

10. Compounds in accordance with claim 1, wherein one of R<sup>1</sup>/R<sup>2</sup> is lower alkyl and  
the other is -CH<sub>2</sub>-C(O)-N(CH<sub>3</sub>)<sub>2</sub> or tetrahydropyran and R<sup>3</sup> is phenyl or pyridinyl, which  
rings are optionally substituted by morpholinyl, halogen or lower alkyl.

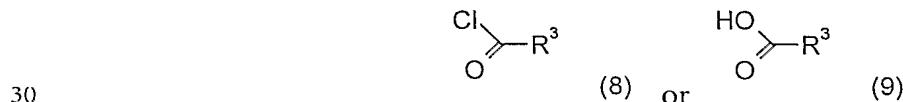
- 15 11. Compounds in accordance with claim 10, wherein the compound is  
*N*-[7-(dimethylcarbamoylmethyl-methyl-amino)-4-methoxy-benzothiazol-2-yl]-4-fluoro-  
benzamide,  
*N*-[7-(dimethylcarbamoylmethyl-ethyl-amino)-4-methoxy-benzothiazol-2-yl]-4-fluoro-  
benzamide,  
20 4-fluoro-*N*-{4-methoxy-7-[methyl-(tetrahydro-pyran-4-yl)-amino]-benzothiazol-2-yl}-  
benzamide or  
*N*-{4-methoxy-7-[methyl-(tetrahydro-pyran-4-yl)-amino]-benzothiazol-2-yl}-2-  
morpholin-4-yl-isonicotinamide.

25 12. A process for preparing a compound of formula I as defined in claims 1 - 11,  
which process comprises

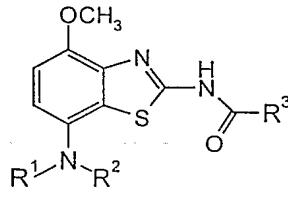
- a) reacting a compound of formula



with a compound of formula



to a compound of formula



wherein R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> are as defined in claim 1, and

- 5 if desired, converting the compounds obtained into pharmaceutically acceptable acid addition salts.

13. A compound according to any one of claims 1 to 11, whenever prepared by a process as claimed in claim 8 or by an equivalent method.

10 14. A medicament containing one or more compounds as claimed in any one of claims 1 to 11 and pharmaceutically acceptable excipients.

15. A medicament according to claim 14 for the treatment of diseases related to the adenosine receptor.

16. The use of a compound in any one of claims 1 to 11 for the treatment of diseases.

17. The use of a compound in any one of claims 1 to 11 for the manufacture of corresponding medicaments for the treatment of diseases related to the adenosine A<sub>2A</sub> receptor.

18. The invention as hereinbefore described.

\*\*\*

## INTERNATIONAL SEARCH REPORT

Inte  
nal Application No  
PCT/EP 02/13770

A. CLASSIFICATION OF SUBJECT MATTER  
 IPC 7 C07D277/82 C07D491/08 C07D417/14 C07D417/12 A61K31/428  
 A61K31/425

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
 IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, BEILSTEIN Data, WPI Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, A	WO 01 97786 A (HOFFMANN LA ROCHE) 27 December 2001 (2001-12-27) abstract examples claims ----	1-18
A	WO 00 18767 A (HE XIAO SHU ;NEUROGEN CORP (US)) 6 April 2000 (2000-04-06) abstract claims examples -----	1-18



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

## ° Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

27 March 2003

Date of mailing of the international search report

07/04/2003

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Stix-Malaun, E

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/EP 02/13770

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:  

Although claim 16 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2.  Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3.  Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.  As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4.  No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
- No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern

nal Application No

PCT/EP 02/13770

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 0197786	A	27-12-2001	AU	8181701 A	02-01-2002
			WO	0197786 A2	27-12-2001
			NO	20025978 A	12-12-2002
			US	2002045615 A1	18-04-2002
<hr/>					
WO 0018767	A	06-04-2000	AU	6280199 A	17-04-2000
			CA	2345944 A1	06-04-2000
			CN	1325397 T	05-12-2001
			EP	1117663 A2	25-07-2001
			JP	2002525373 T	13-08-2002
			WO	0018767 A2	06-04-2000